Community Detection of Non-Ischemic Stage B Heart Failure

By

Hong Yang (Hilda)

BMed

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The research work presented in this thesis was supervised by:

Primary supervisor

Professor Thomas H Marwick, MBBS PhD MPH

Menzies Institute for Medical Research Tasmania

University of Tasmania

Hobart, Australia

Baker-IDI Heart and Diabetes Institute

Melbourne, Australia

and

Co-primary supervisor

Dr Kazuaki Negishi, MD PhD

Menzies Institute for Medical Research Institute Tasmania

University of Tasmania

Hobart, Australia

Declaration of originality

This thesis contains no material which has been accepted for a degree or diploma by the University or any other institution, except by way of background information and duly acknowledged in the thesis, and to the best of my knowledge and belief no material previously published or written by another person except where due acknowledgement is made in the text of the thesis, nor does the thesis contain any material that infringes copyright.

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Name: Hong Yang (Hilda)

Signed: ……………………………   Date:.…25/11/2016……

Statement of ethical conduct

The research activities associated with this thesis complied with "Australian Code for the Responsible Conduct of Research", "National Statement of Ethical Conduct in Human Research", "Guidelines for the prevention, detection and management of Chronic heart failure in Australia 2011", and Regulator and the rulings of the Safety, Ethics and Institutional Biosafety Committees of the University.

The Tasmania Human Research Ethics Committee (HREC) approved this project (Approval number H0013333, Tasmanian Study of Echocardiographic detection of Left ventricular dysfunction-TasELF). We obtained written participant informed consent from all participants.

Name: Hong Yang (Hilda)

Signed: ……………………………… Date: ….25/11/2016……

Abstract

Background. Stage B Heart Failure (SBHF) is an early stage with no symptoms but evidence of cardiac impairment. It is difficult to diagnose and manage without echocardiography (Echo, ultrasound of the heart), and the availability of this test in primary care and in rural areas is very limited. To date, there is no effective screening strategy for the identification of non-ischemic SBHF. There is also no evidence available on the efficacy of treatment of this condition to reduce outcome events.

Aims. This research aimed to study the following: 1) how to assess heart failure (HF) risks clinically (before echocardiogram); 2) what screening tools to use; 3) how to develop a community screening program combining cardio-protective therapy in at-risk elderly individuals; 4) to define the best strategies in community screening, including the role of electrocardiogram (ECG) versus Echo; 5) to identify the best echo predictors (advanced versus conventional echo markers) for outcome at 1 year follow up; 6) to investigate the benefits of an intervention response based on imaging guided care versus usual care - randomized controlled trial; 7) to investigate the benefit of community screening in a young population and association with childhood adiposity.

Methods. A systematic review and meta-analysis was performed to identify possible clinical markers to be used to select subjects at high risk of HF for echo in the community. A method validation study was performed on comparing strain measurement variabilities between and among vendors as well as software versions. Data from CDAH3 pilot trial (Childhood Determinants of Adult Health) was used to assess the association of childhood adiposity and evidence of SBHF in a young population. An important study platform for this research was the Tasmanian Study of Echocardiographic Detection of Left Ventricular Dysfunction (TasELF). Between 9/2013 and 11/2015, a total of 1026 community individuals responded to our study advertisement. Of these, 618 stage A HF individuals met inclusion criteria and were eligible (mostly hypertension, diabetes and obesity). At baseline, participants underwent standard clinical evaluation, anthropometry, blood pressure, functional capacity using 6-minute walk test, 12-lead ECG and comprehensive echo assessment. Four ECG markers were assessed including Cornell Product (Cornell-P), P wave terminal force in lead V1 (PTFV1), ST depression in lead V5 V6 (minSTmV5V6) and increased heart rate. Four echo markers were used to define the presence of SBHF, including left ventricular hypertrophy (LVH), left atrial enlargement (LAE), impaired E/e' or impaired global longitudinal strain (GLS). Participants were then randomized into two arms: imaging guided care using advanced echocardiography (AE arm, including myocardial deformation and detailed diastolic function examination) or usual care (UC arm). The presence of abnormal findings was used to justify subsequent cardio-protective treatment. A process evaluation was conducted at 3 months, and adherence to therapy was assessed. Patients were followed for 1 year for outcome. The primary composite end point was new HF and death from cardiovascular causes.

Results. First, prediction of incident HF can be calculated from 7 common clinical variables (age, gender, BMI, smoking, hypertension, diabetes and coronary artery disease). **Second**, the strain measurement variability has improved after the joint standardization task force, is analogous to that of ejection fraction and can be used widely. **Third**, cardiac impairment was present in otherwise healthy but overweight and obese young adults. Cardiac impairment was associated with adult body adiposity but not with childhood adiposity. **Fourth,** comparing with patients with hypertension, patients with diabetes had more impaired global longitudinal strain (GLS) and reduced 6-minute walk test distance. Hypertensive patients had more impaired diastolic function. **Fifth,** abnormal ECG markers showed low sensitivity for SBHF but were associated with poor outcome in those with early cardiac impairment. **Sixth,** the overall annualized incident rate for new HF was 10% in these elderly individuals at risk of HF. The initial clinical risk assessment combing functional assessment facilitated effective HF screening by identifying the high and intermediate risk groups for echocardiographic screening. **Seventh**, the prevalence of SBHF was **62%** defined by the presence of ≥ 1 of the four echo markers (LVH, LAE, impaired GLS and abnormal E/e'). These markers were associated with outcome. The presence of ≥ 1 of any of four SBHF markers was associated with more than 3-fold higher risk. Impaired GLS was a more sensitive marker and provided incremental value over clinical information for prediction. **Eighth**, imaging guided cardio-protective therapy was ineffective with only 43% having treatment up-titration and 9% reaching target dose. At 1 year follow-up, the incidence of HF was no different between two arms. Among subjects needing therapy on the basis of imaging and adherence to therapy, imaging guided care showed a 77% lower hazard for outcome. Participant non-adherence to treatment was a potential obstacle in HF prevention in patients with SBHF. Attitude to additional therapy seemed the main barrier to success of cardio-protection of SBHF. At 1 year follow-up, the trial was stopped for futility.

Conclusions:

Screening for SBHF in the community using echocardiography was feasible. Given the high annualized incident rate of new HF and the recognized adverse outcome of SBHF, the identification of those at higher risk was important. However, the adherence to preventive therapy was low. In order to reduce the burden of heart failure, effort needs to be made not only to identify but also to initiate effective preventive treatment.

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List of abbreviations

2D:	two-dimensional
6MW:	Six-minute walk test
A:	peak trans-mitral A velocity, reflects the pressure gradient during atrial contraction
ACEi:	Angiotensin-Converting Enzyme
AF:	atrial fibrillation
AIC:	Akaike’s Information Criterion
ANP:	atrial natriuretic peptide
BB:	beta-blocker
BMI:	body mass index
BNP:	brain natriuretic peptide
CAD:	coronary artery disease
CV:	cardio-vascular walk
CART:	classification and regression tree
Cornell-P:	Cornell Product
CRP:	C reactive protein
DecT:	deceleration time
DD:	diastolic dysfunction
E:	peak trans-mitral E velocity, correlates with early rapid filling gradient
e’:	peak early mitral annular tissue Doppler velocity
ECG:	electrocardiogram
Echo:	echocardiogram
E/e’	mitral inflow peak early diastolic velocity/tissue Doppler early diastolic velocity
EF:	ejection fraction
ESC:	European Society of cardiology
GLS:	global longitudinal strain
GCS:	global circumferential strain
HF:	heart failure
HFpEF:	heart failure with preserved ejection fraction
HFrEF:	heart failure with reduced ejection fraction
HHE:	hand held echocardiography

HTN:	hypertension
LA:	left atrium
LAVi:	left atrium volume index
LAE:	left atrium enlargement
LV:	left ventricle
LVEF:	left ventricular ejection fraction
LVH:	left ventricular hypertrophy
LVM:	left ventricular mass
LVMi:	left ventricular mass index
minSTmV5V6:	minimal ST depression in lead V5 V6
miRNA:	micro RNA
NT-pro BNP:	N-terminal proBNP
NRI:	net reclassification improvement
PTFV1:	p wave terminal force in lead V1
RWT:	relative wall thickness
SAHF:	stage A heart failure
SBHF:	stage B heart failure
ST2:	cardiac biomarker member of the interleukin 1 receptor family
T2DM:	type 2 diabetes

List of publication and Statement of authorship

This thesis includes several papers, in which Hong Yang (HY) is not the sole author. HY took the lead in this research. She designed the studies, collecting the data, measuring echo parameters, performed analyses, interpreted the findings and prepared the manuscripts, with contributions from the co-authors.

The contributions of each of the authors in the 8 publications listed are detailed as follows.

Chapter 2:

Yang H, Negishi K, Otahal P, Marwick TH. Clinical prediction of incident heart failure risk: a systematic review and meta-analysis. Open Heart 2015;2: e000222.

The contributions of each author are as following:

- HY contributed to study design, data extraction, performing analyses, interpreting findings, composed the drafts of manuscript and revisions of the manuscript.
- KN contributed to data extraction, interpretation of finding and revised the manuscript
- PO contributed to data extraction, provided statistical expertise analysis and revised the manuscript
- THM contributed to the design of the study, interpreting findings, critically revision and final approval.

Chapter 4:

Yang H, Marwick TH, Fukuda N, Oe H, Saito M, Thomas JD, Negishi K. Improvement in Strain Concordance between Two Major Vendors after the Strain Standardization Initiative. J Am Soc Echocardiogr 2015; 28:642-648.e647.

The contributions of each author are as following:

- HY contributed to study design, data collection, performing analyses, interpreting findings, composing the drafts of manuscript and revisions of the manuscript.
- THM contributed to study design, interpretation of finding and critical revision of the manuscript
- NF contributed to data acquisition and revised the manuscript
- HO contributed to data acquisition and revised the manuscript
- MS contributed to data acquisition and revised the manuscript
- TJD contributed to critical manuscript revision.

- KN contributed to the design of the study, performing analysis, interpreting findings, critical revision and final approval for submission.

Chapter 5:

Yang H, Huynh L Q, Venn AL, Dwyer T, Marwick TH. Associations of Childhood and Adult Obesity with Left Ventricular Structure and Function. Int J Obes (Lond). 2017; 41 (4): 560-568.

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- HY contributed to study design, data collection, performing analyses, interpreting findings, composing the drafts of manuscript and revisions of the manuscript.
- QHL contributed to study design, performing analyses, interpreting findings, and revision of manuscript
- ALV contributed to interpretation of finding and critical revision of the manuscript
- TD contributed to revision of manuscript
- THM contributed to the design of the study, interpreting findings and critical revision and final approval for submission.

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Chapter 7:

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- YW contributed to data collection and revision of manuscript
- MN contributed to data collection and revision of manuscript
- KN contributed to data collection, revision of manuscript
- FK contributed to data collection, analysis
- PMO contributed to study design, data collection, interpreting findings and critical revision of the manuscript

<u>Chapter 8</u>:

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- PMO contributed to interpretation of results and revision of manuscript
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<u>Chapter 9</u>:

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Chapter 10:

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- THM contributed to the design of the study, data collection, interpreting findings, critical revision and final approval of the manuscript for submission.

Signed by candidate and primary supervisor

Candidate: Hong Yang (Hilda)

Signature: ………………………………………. Date: …25/11/2016…………………

Professor Thomas H Marwick

Signature: ______________________________Date: 25 NOV 2016

Chapter 1

Introduction

Chapter 1. Introduction

1.1 The Magnitude of Heart Failure

1.1.1 Worldwide

The incidence and prevalence of heart failure are growing and assuming epidemic proportions, affecting an estimated 23 million people worldwide[20] [21] and 5.7 million new cases each year[20]. In the United States, 5 million people suffer from heart failure, with a rate of 550,000 new cases diagnosed each year[22]. Heart failure is predominantly a problem of old age; 80% of patients with incident heart failure are older than 65 years and 50% are older than 80 years[23].

Heart failure is major burden to the health care system and to the community due to the cost of care and poor quality of life. The total direct and indirect cost of heart failure in US exceeds $30 billion [24], where it accounts for 12-15 million office visits and 6.5 million hospital days each year [25]. In the United States, approximately $2.9 billion annually is spent on drugs for the treatment of heart failure[25].

1.1.2 Australia

In Australia, the overall prevalence of heart failure is estimated to be 2-3%. The prevalence is 23% in those aged over 65 years; 570,000 people are living with heart failure and 30,000 Australians receive a new diagnosis of heart failure each year[26]. More than 45,000 Australians were hospitalized due to heart failure in 2009-2010, equating to over 360,000 bed days.

The cost of chronic heart failure in Australia has been estimated at over $ 1 billion per year[27].

1.1.3 Challenges

With the magnitude of the disease, the question is whether the burden of clinical heart failure can be prevented or delayed at an early stage. If yes, how can we identify patient who need to be targeted for heart failure prevention and what are the effective tools for early detection? Besides treating and controlling heart failure risk factors, what is the current evidence on pharmacological treatment of cardiac dysfunction to improve outcome? This chapter will mainly summarize the current evidence and evidence gaps to address these challenges.

1.2 Heart Failure Definition Diagnosis and Classification

1.2.1 Definition

Heart failure is a complex clinical syndrome that is frequently, but not exclusively, characterised by an underlying structural abnormality or cardiac dysfunction that impairs the ability of the left ventricle (LV) to pump or to fill blood, particularly during physical activity. Symptoms of heart failure (e.g. dyspnoea and fatigue) can occur at rest but are more common during physical activity[28].

1.2.2 Diagnosis

Heart failure is a clinical diagnosis. In hospital setting, this involves an initial evaluation including a history and physical examination, chest radiography, electrocardiography, and laboratory assessment to identify causes or precipitating factors. No single item on clinical history, sign, or symptom has been proven or can be used to diagnose heart failure.

The recognition of heart failure in a primary care level can be more difficult. Because of comorbidity and atypical clinical manifestations, the diagnosis is particularly challenging in older persons. There are several diagnostic instruments including Framingham[29], Boston[30], Gothenburg criteria [31]and the European Society of Cardiology (ESC) principles[32]. Among these, the Framingham criteria are widely accepted[33]. It included the components of the initial evaluation mentioned above. The Framingham heart failure diagnostic criteria are displayed in Table 1.1.

Table 1.1 Framingham clinical diagnostic congestive heart failure

Major criteria:

- Paroxysmal nocturnal dyspnoea or orthopnoea
- Neck vein distension
- Rales
- Cardiomegaly
- Acute pulmonary oedema
- S3 gallop
- Hepatojugular reflex

Minor criteria:

- Ankle oedema
- Nocturnal cough
- Dyspnoea on exertion
- Hepatomegaly
- Pleural effusion
- Tachycardia (>120 beat per minute)

1.2.3 Classification

The diagnosis of overt heart failure (HF) requires clinical symptoms. With the hope that early recognition and treatment may prevent the progression of disease, two early asymptomatic stages have been classified in the "Guidelines for the Diagnosis and Management of HF in Adults" by the American College of Cardiology (ACC) and the American Heart Association (AHA) [25]. **Stage A heart failure (SAHF)** is identified in patients who are asymptomatic but with HF risk factors including hypertension, atherosclerotic disease, diabetes mellitus, obesity, metabolic syndrome (MS), previous exposure to cardiotoxins or with a family history of cardiomyopathy. **Stage B heart failure (SBHF)** is identified in patients who have evidence of structural heart disease, but remain asymptomatic. This includes patients with previous myocardial infarction, left ventricular remodelling including hypertrophy and reduced ejection fraction and valvular diseases. Stages C and D include patients in clinically overt heart failure with marked symptoms and require medical intervention and/or with frequent hospital admission and readmissions[25].

Once the diagnosis is established, HF can be subdivided according to the type of left ventricular dysfunction. Echocardiography is the most useful test for this purpose. Systolic heart failure refers to a weakened ability of the heart to contract. Diastolic heart failure refers to impaired filling of the LV in response to a volume load, despite normal ventricular contraction and is classified as “diastolic heart failure”. Systolic and diastolic heart failure can occur together but the distinction between them is relevant to the therapeutic approach.

1.2.4 Preclinical heart failure

Stage A and stage B are precursor stages of clinical heart failure. The distinction of stages A and B is important as their treatment strategy and therapeutic implications are different. The therapeutic strategy of stage A HF (SAHF) is mainly the control of underlying risk factors, i.e. hypertension and diabetes and metabolic syndrome, although specific therapy using ACEi or ARB is only indicated in those patients on the basis of T2DM or vascular disease.

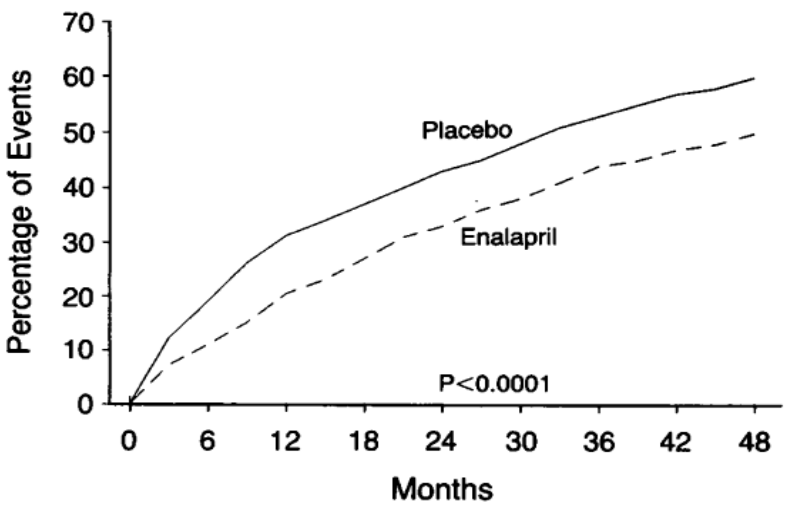


Figure 1.1 Treatment efficacy of stage B heart failure (SOLVD)
Adopted from SOLVD investigators N England Journal of Medicine, 1991; 325(5)

The main recommendation for treating SBHF is the use of angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) and beta-blockers[25]. These agents have been proven to be beneficial in clinical randomized contrail trials (RCT) and widely accepted for outcome benefit in general [34]. In the trials of Study of Left Ventricular Dysfunction (SOLVD)[35,36] and Survival and Ventricular Enlargement (SAVE)[37,38] of patients with asymptomatic LV dysfunction, ACEi or ARB and beta blockers were beneficial in all stage B patients, with mortality and morbidity decreased by 20-30%[37-42] (Figure 1.1).

1.2.5 Evidence gaps (the non-ischaemic population)

Ischaemic SBHF refers to patients with previous coronary artery disease or the presence of echocardiographic evidence of scar or regional wall motion abnormalities. Clinically, ischaemic SBHF may progress to heart failure with reduced ejection fraction (HFrEF).

Non-ischaemic SBHF may occur in patients with hypertension, diabetes, obesity, metabolic syndrome and previous exposure to cardio-toxic agents and patients with familial history of cardiomyopathy, without a known history of coronary artery disease. They often have normal left ventricular systolic contraction and progress to clinical heart failure with preserved ejection fraction (HFpEF). Thus, while, SBHF is readily defined in patient after myocardial infarction with reduced left ventricular ejection fraction, its recognition in non-ischaemic disease is more challenging.

Previous efforts in screening and management of early HF have been largely devoted to patients with coronary artery disease. However, the epidemiology of heart failure is changing, with increasing numbers of patients with normal left ventricular ejection fraction.

In the community, non-ischaemic SBHF is highly prevalent in the elderly and largely undetected. It needs to be noted that these individuals with cardiac dysfunction in the community would not have been eligible for the clinical trials like SOLVD and SAVE, in which middle-aged subjects with coronary artery disease and moderate to severely reduced LV ejection fraction (LVEF<40%) dominated. There are currently few clinical data focusing on benefit of early recognition and intervention in non-ischaemic population with relatively preserved LV ejection fraction[34].

Thus, there are evidence gaps in the early recognition and intervention of non-ischaemic SBHF in the population. The implications of treating these common forms of SBHF (identified by abnormal geometry or diastolic dysfunction[25] but not by standard criteria by ejection fraction) for the entire health care system are have not been defined.

The approach to community screening and early intervention of non-ischaemic SBHF is the focus of this thesis.

1.3 Stage B heart failure

1.3.1 Prevalence and natural history

SBHF is a preclinical stage. Patients may be detected coincidently, when they present with other problems, or screening in the community. This is the target population that will potentially be benefit from early intervention. Although highly prevalent, the prevalence in the community is dependent on how closely we look –i.e. the imaging modality or imaging markers. The conventional markers of SBHF are impaired left ventricular ejection fraction (LVEF), left ventricular hypertrophy (LVH) and diastolic dysfunction. Community studies using echocardiographic assessment have provided the prevalence and natural history of SBHF[2,43-50]. The prevalence of asymptomatic left ventricular systolic dysfunction by ejection fraction (LVEF≤50%) was 3-7% and higher in the elderly (>65 years) [43,49]. The incident rate of new heart failure in these patients was reported to be 5.7-5.8 per 100 person-years as compared with 2.4 per 100 person-year years in those with normal LVEF[51,52].

The prevalence of LVH was reported to be 16-30%[53,54]. Patients in the highest left ventricular mass quintile showed a relative risk of 2.8 for incident heart failure over 5.5 years follow up[54]. The regression of LVH was reported to be associated with reduced events[54] independent of ischaemic process[55] and independent of the initial measurement of left ventricular mass [50].

Patients with diastolic dysfunction (DD) are a complex group. The prevalence of DD varies with DD grade and among patients with different risk groups. In elderly (>65 years) with a diagnosis of hypertension or coronary disease, mild diastolic dysfunction was reported 36% and more severe forms of DD in 16%[56]. This prevalence was reported to be 20-30% in patients with obesity and diabetes [57-59]. The nature history of DD depends on disease stage. From et al. reported that five year incident heart failure was 36.9% in moderate DD (using mitral E/e'>13) compared with those normal diastolic function[57] Figure 1.2**.** The overall mortality of stages of diastolic dysfunction is reported by Redfield [43]from the Framingham cohort and displayed in Figure 1.3.

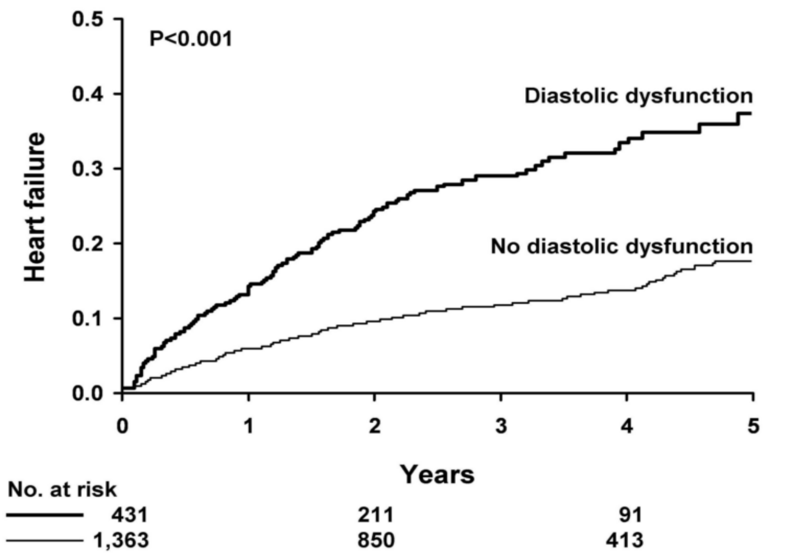


Figure 1.2 Kaplan-Meier analysis of diastolic dysfunction
Diastolic dysfunction and subsequent heart failure in diabetic patients
Adopted from From et al. JACC 2010; Jan 26; 55(4): 300-5

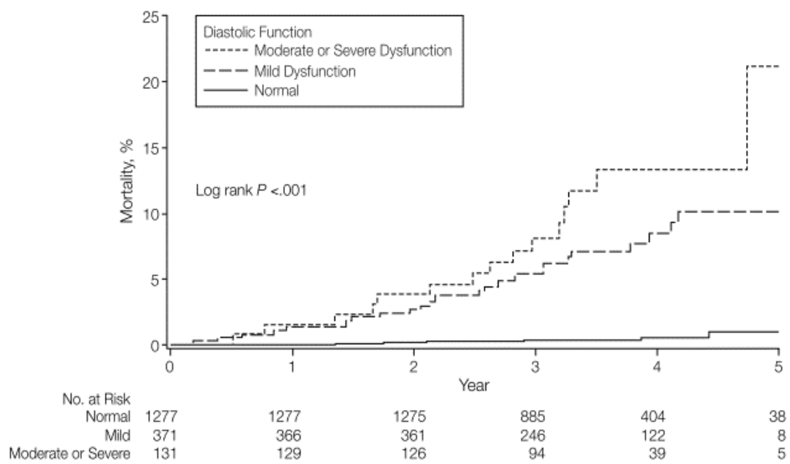


Figure 1.3 Natural history of diastolic dysfunction
Kaplan-Meier mortality curves for participants with normal diastolic function versus mild, moderate and severe diastolic dysfunction.
Adopted from Redfield et al. JAMA 2003; 289 (194-202)

The overall prevalence of heart failure stages in the community was studied and reported by Ammar (Figure 1.4)[44]**.** The corresponding outcome and survival status relating to each stage is also shown in Figure 1.4.

HF Stage	45–54 y	55–64 y	65–74 y	≥75 y	Total
0	281 (46.9)	225 (36.0)	107 (20.9)	27 (9.3)	640 (31.5)
A	167 (27.9)	157 (25.1)	94 (18.3)	36 (12.3)	454 (22.4)
B	138 (23.0)	202 (32.3)	237 (46.2)	114 (39.0)	691 (34.1)
C	13 (2.2)	41 (6.6)	74 (14.4)	111 (38.0)	239 (11.8)
C_1	9 (1.5)	32 (5.1)	65 (12.7)	89 (30.5)	195 (9.6)
C_2	4 (0.7)	9 (1.4)	9 (1.8)	22 (7.5)	44 (2.2)
D	0 (0)	0 (0)	1 (0.2)	4 (1.4)	5 (0.2)
Total	599	625	513	292	2029

Data are presented as number of persons (column percent).

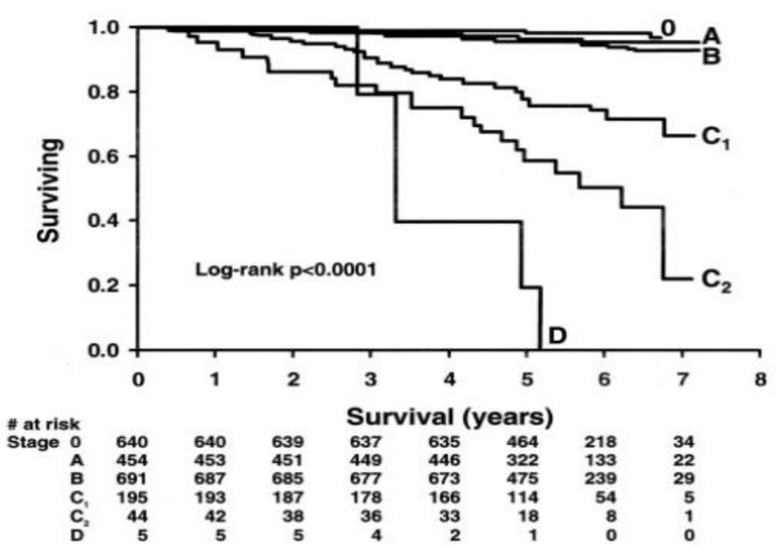


Figure 2. Survival curves according to HF stage.

Figure 1.4 Prevalence of heart failure stages
Prevalence of heart failure stages and related outcome in the community
Tables and figures adopted from Ammar et al. Circulation; (115):1563-70, 2007.

1.3.2 Identification of Stage B heart failure

Identification and diagnosis of SBHF requires imaging – usually echocardiography. SBHF is relatively easy to identify in the ischaemic population as echocardiography is clinically indicted in this population. Echocardiographic markers are evidence of myocardial scar after infarction or reduced left ventricular ejection fraction or the presence of both. The identification and diagnosis of non-ischaemic SBHF patients can be difficult. Left ventricular ejection fraction is often preserved and is unsuitable for this population. Approximately half of heart failure patients have preserved LVEF (HFpEF) [60]. Diastolic dysfunction is an early marker of myocardial relaxation and filling status, especially in the non-ischaemic population due to the high prevalence of hypertension and diabetes. However, conventional assessment of diastolic dysfunction needs assessment of several parameters including colour Doppler, pulsed Doppler of mitral inflow, pulmonary and myocardial tissue velocity and the size of left atrium. Cardiac rhythm and loading issues are other factors complicating the grading. Therefore, the integrated diastolic functional grading can be indeterminate as these assessments are often discordant[61].

Speckle tracking echocardiography (STE) for the measurement of myocardial deformation and strain is a relatively advanced imaging modality. It is a semi-automated and quantitative technique for the measurement of left ventricular long-axis, circumferential and radial function[62,63]. The details of STE technology will be discussed **in Chapter 3 (Methods)**.

Among the STE markers, global longitudinal strain (GLS) has been adopted in routine clinical practice and is increasingly accepted as a feasible and useful marker. GLS has shown to be a sensitive marker over left ventricular ejection fraction for early myocardial impairment and a better marker of prognostic value[64-67], especially with preserved left ventricular ejection fraction and without wall motion abnormalities. Furthermore, GLS corresponds to a variety of parameters that reflect the presence of fibrosis[68,69]. These changes are linked to the underlying metabolic disturbances associated with stage A heart failure risks[68].

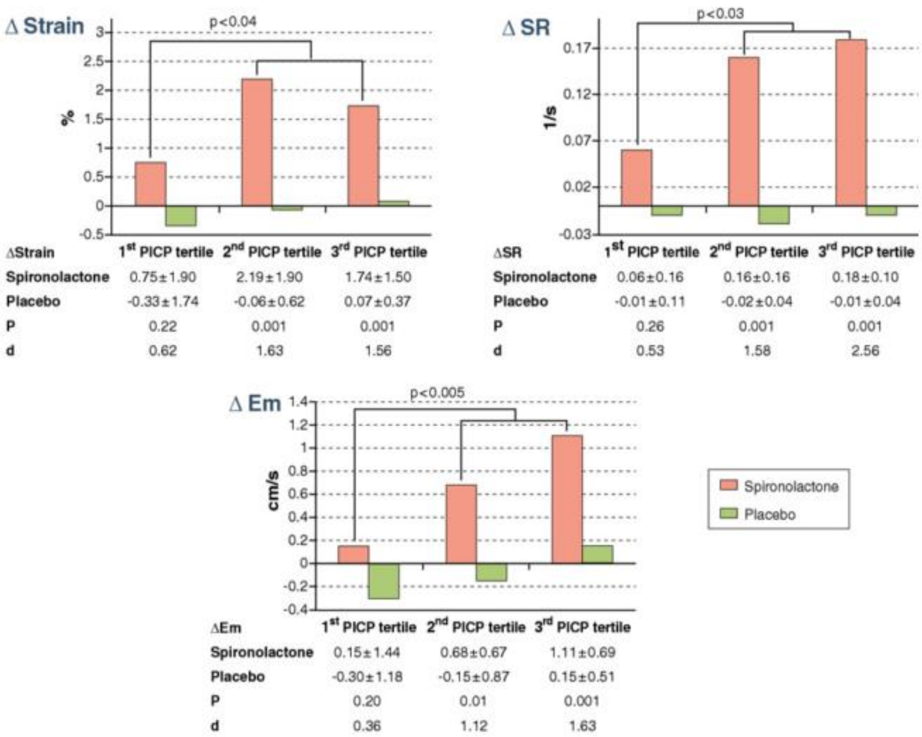


Figure 1.5 Improved GLS after intervention
Left ventricular function improve after intervention.
Figure adopted from Kosmala et al. JACC Cardiovascular imaging 2011; 4 (12):1239-49.

Because of the prognostic value of DD and GLS, there have been proposal to extend the definition of SBHF from conventional markers including LVEF and LVH to impaired myocardial deformation and (GLS) diastolic dysfunction based on functional assessment[70]. As a potential modifiable marker, GLS has been reported to be associated with treatment response in various settings[71-73]. These studies showed evidence that left ventricular myocardial impairment may be reversible at this early stage (Figure 1.5).

Other means of identification of SBHF are non-echocardiographic approaches. The concept of non-echocardiographic detection and screening of left ventricular systolic dysfunction is largely based on feasibility of the test and cost-effectiveness strategy[74]. This includes a variety of cardio-specific biomarkers, electrocardiography, and hand-held echocardiography. The implication of non-echocardiographic approaches to assessment of SBHF will be discussed in **Chapter 2 (Clinical Prediction of Incident Heart Failure Risk)**.

1.4 Community Screening for Stage B heart failure

Community screening for SBHF is based on the belief that early identification and early intervention may delay or prevent its progression to overt heart failure. SBHF is known to be highly prevalent in the community. Screening in the community seeks to detect disorders in seemingly healthy persons. The key research question is "Will screening in the seemingly normal individuals do more good than harm**?**"

1.4.1 Guidelines to determine community screening effectiveness

In order to assess the value of community screening programs, seven criteria should be satisfied[75]. Such criteria are informative in the approval of screening programs by organizations such as the US Preventative Services Task Force (USPSTF). They evaluate and make recommendations regarding screening services in the community[76].

The seven criteria are as following:

1. Has the effectiveness of the program been demonstrated in a randomized trial?

   (If an effectiveness trial with a positive result has not been carried out, then the following are pertinent):

2. Are efficacious treatments available?
3. Does the burden of suffering warrant screening?
4. Is there a good screening test?
5. Does the program reach those who could benefit from it?
6. Can the health system cope with the screening program?
7. Will those who had a positive screening comply with subsequent advice and interventions?

To date, there have been no randomized trials evaluating the impact of a strategy to screen and treat for SBHF[77]. There is also insufficient evidence on: 1) what is a good screening test/or screening strategy for detection of non-ischaemic SBHF; 2) whether a screening program can reach those individuals at high risk of heart failure and who may be benefit from early intervention; 3) most importantly, whether those who had a positive screening will comply with subsequent advice on interventions; 4) Lastly, it is unknown whether the health system can cope with the screening program of SBHF.

This thesis seeks to explore, evaluate and gather evidence to address the criteria 1, 2, 4, 5 and 7.

1.4.2 Who to screen

The recognition of SBHF needs echocardiography. One of the main concerns is the cost of the test and its feasibility in the community settings. Rather than screen the whole population at large, screening may be most feasible and effective if applied to selected individuals of higher risk. "Who to screen" and whether a "screening program can effectively reach those who could benefit" are the important first steps.

Clinical risk factor-based screening would identify people at higher risk. There have been a few heart failure risk scores derived from population studies. They are the Atherosclerosis Risk in Communities (ARIC) heart failure risk score[78]; the Health ABC heart failure risk score[79] and the Framingham heart failure risk scores with and without the consideration of biomarkers[80,81]. However, these scores were developed in selected study populations and some require the use of bio-markers, which are potential limitations in the community setting. Readily available clinical information could be combined into a possible risk algorithm tool to facilitate selection of "who to screen" in the community.

The clinical prediction of incident heart failure risk is summarized in **Chapter 2** (the following chapter). The feasibility and performance of these risk scores will be further explored in **Chapter 8** (Screening strategy- role of HF scores ECG and 6MW).

1.4.3 How to screen

After selection of the "at risk" individuals, comprehensive echocardiography is considered the single most useful diagnostic test in patients with suspected HF. This test evaluates and determines whether abnormalities of myocardium, heart valves, or pericardium are present and which chambers are involved[25]. In asymptomatic community individuals, unselective screening using echocardiography was not justified due to the cost of the test and relative low prevalence of the conditions [47,82]. In these studies, the main echocardiographic marker for SBHF was reduced LVEF. LVEF is not a suitable marker to detect non-ischaemic SBHF, and the prevalence of reduced LVEF in the community was low[82]. Screening of non-ischaemic SBHF requires more sensitive tools and has been facilitated by the use of speckle tracking echocardiography (STE) of myocardial deformation (strain) and diastolic functional assessment[70]. The implications of STE and GLS as sensitive markers to identify SBHF has been discussed in the previous section.

In the community setting, measurement of segmental and global longitudinal strain (GLS) has been reported in healthy individuals[83]. Although, the normal ranges for global longitudinal strain (GLS) has been defined and widely used [84,85], its value in the community in improving outcome is predicated on the ability to combine modified therapy and has not been proven.

Another main concern of using GLS for community screening and subsequent intervention is its measurement variability[86]. The measurement variability between vendors and software versions is often cited as a limitation to the clinical application. To achieve a consensus on methodology for the quantitative evaluation of cardiac mechanics, the European Association of Cardiovascular Imaging and the American Society of Echocardiography (ASE) has implemented a standardization initiative to improve and reduce inter-vendor variability. Whether there has been improvement in this aspect ensure this new imaging modality robust enough to be used for screening will be discussed in **Chapter 4** (Use of Strain for Screening – is it Robust Enough?)

1.4.4 Implication of treatment

The evidence of pharmacological treatment benefit for asymptomatic left ventricular dysfunction has been document in a few important clinical trials. These trial are: the Study of Left Ventricular Dysfunction (SOLVD); the Survival And Ventricular Enlargement (SAVE) trial; the Carvedilol Post-infarct Survival Control in LV Dysfunction (CAPRICORN) trial; the Australia/New Zealand (ANZ) trial; the Reversal of Ventricular Remodelling with Toprol-XL (REVERT) trial; the Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL); the TRAndolapril Cardiac Evaluation (TRACE) trial; and the Valsartan in Acute Myocardial Infarction Trial (VALIANT)[37,38,40,87-94].

Most of these studies used reduced LVEF (<35-40%) as marker of SBHF and the use of ACEi or ARB and beta blocker showed outcome benefit[40,91]. The number needed to treat (NTT) ranged from 8-48[34]. Based on evidences summarized in a systematic review, it was suggested that ACE inhibitors (or ARBs in those with a history of intolerance to ACE inhibitors) should be administered to all patients with asymptomatic LV dysfunction in the absence of contraindications. Beta blockers should also be considered in the vast majority of patients, although evidence to support their use is less robust[34].

Given that the benefit of treatment in left ventricular systolic dysfunction has been established and accepted in the ischaemic SBHF, there are uncertainties: 1) whether those with mild LVSD would benefit similarly from treatment as they would not have been eligible for the trials like SOLVD or SAVE; 2) treatment of non-ischaemic forms of SBHF (LVH or diastolic dysfunction) is not well defined; 3) How these cardio-protective therapies should be up-titrated in those who are already on these agents for their primary risk factors or combined with other treatments; 4) treatment adherence in these asymptomatic populations, whether they will comply with subsequent interventions in the case of abnormal screening.

The intervention response to screening result will be evaluated and discussed in **Chapter 10** (Therapeutic Guidance from Screening).

1.4.5 Potential Issues of community screening for stage B heart failure

Screening in asymptomatic adults causes concerns that “disease labelling” and “medicalization”, which may cause psychological distress and anxiety. However, these effects may be minimal. The spectre of cardiovascular disease is familiar in these individuals with conditions like diabetes, metabolic syndrome and hypertension. Since the risk of false positives will lead to over-treatment; while the risk of limited test sensitivity may lead to false negative, resulting in delayed treatment. However, we lack evidence on whether the detection of SBHF changes management or outcome[76].

To date, screening for heart failure has not been recommended by the US Preventive Services Task Force (USPSTF) [76] and few screening tests for cardiovascular disease have been endorsed by the USPSTF (http://www.uspreventiveservicestaskforce.org).

Some of these issues will be discussed in the subsequent chapters.

1.5 Aims of this thesis

The Aims of the thesis are based on the following established facts: 1) Heart failure is an increasing health care burden in Australia – being among the most frequent causes of hospital admissions[95]. 2) Elderly subjects with diabetes, hypertension, obesity, past cancer therapy or known cardiac disease are at particularly higher risk of developing non-ischaemic heart failure[25]. 3) If identified early, treatment of non-ischaemic SBHF is hoped to prevent or delay its progression to overt HF[34,37,38]. 4) Echocardiography is the most important test to identify non-ischaemic SBHF[96]. Advanced echocardiographic imaging modalities are able to identify early myocardial damage and show excellent prognostic values[73,84,97].

Therefore, the main aims are to determine the value of echocardiographic screening in the community to identify non-ischemic SBHF and to guide subsequent cardioprotective therapy. We also sought to understand the benefit of imaging surveillance to reduce the progression of cardiac dysfunction to overt heart failure with pharmacological treatment. In order to achieve that, the studies presented in this thesis aim to address the following. This list is in similar order of thesis chapters and is aimed to address the following two main aspects: 1) issues related to screening: who to screen, how to screen, what tools to use and what is the best tool; 2) issues related to randomized controlled trial: what is the intervention response to screening results.

- Who to screen – how to assess heart failure risk clinically to select patient for echocardiography
- What screening tools to use – validation of echo strain as a robust marker
- Community screening in a younger age group – association of childhood adiposity and adult subclinical cardiac function (This chapter seeks to assess whether childhood adiposity be used as risk factor in community screening)
- To develop a community screening program combined with cardio-protective therapy
- What is the best screening tool to use – is a combined imaging-marker approach (strain and diastolic functional measures) more appropriate? Are there any association of HF aetiology with echocardiographic features?

- Screening strategy – role of ECG techniques and association with echocardiographic markers and outcome
- Screening strategy – role of risk scores, ECG and baseline function capacity to justify a good pre-screening approach before echocardiographic screening
- Community screening using echocardiography – what are the best echo predictors for outcome
- Community screening and intervention – intervention response to imaging guided care (randomized controlled trial)

1.6 Structure of this thesis

Chapter 1:	Introduction – review of current literature on evidence and evidence-gaps
Chapter 2:	Prediction of incident heart failure – systematic review of clinical risks for incident HF and role of biomarkers
Chapter 3:	Methods – TasELF study protocol and echocardiographic outreach screening clinics; standard Echo; ECG; questionnaires; 6MW test protocols
Chapter 4:	Use of strain for screening – Is it robust enough for screening
Chapter 5:	Community screening in a younger age group – Importance of childhood and adult obesity and associated early cardiac impairment
Chapter 6:	Using combination of screening tools – Association of etiology and pathophysiology
Chapter 7:	Screening strategy in the community – Role of ECG in initial screening, association with echo features of SBHF and outcome
Chapter 8:	Screening strategy in the community – Role of clinical risk scores, ECG and functional assessment (6MW)
Chapter 9:	Community screening using echo – Echocardiographic predictors for outcome (comparison of echo markers)
Chapter 10:	Randomized controlled trial – Interventional response to screening results
Chapter 11:	Summary and conclusions

1.7 Sources of data used in this thesis

Data used for analyses in most Chapters (except for chapter 4 and chapter 5) were from the on-going Tasmania Study of Echocardiographic Detection of Left Ventricular Dysfunction (TasELF). The research protocol was approved by the Tasmanian Human Research Ethics Committee (HREC: H0013333), and registered with the Australian and New Zealand Clinical Trials Registry (http://www.anzctr.org.au/ ; ACTRN12614000080628).

Chapter 4 used 82 patients and healthy adults, data were from the following: 1) outpatient from Royal Hobart Hospital echocardiographic laboratory (n=45), Hobart Australia. 2) Inpatient and outpatient (n=21) and health volunteers (n=16) from Takasaki General Medical Centre, Japan. Data were prospectively collected. Both institutional review boards approved the study protocol.

Chapter 5 used data from the Childhood Determinants of Adult Health (CDAH3) pilot trial. The CDAH3 pilot trial is a 29-year follow up of Australian Schools Health and Fitness Survey (ASHFS) of 8498 Australian Schoolchildren aged 7-15 years in 1985. A sub group of 205 health adults completed a pilot follow trial in 2014. Among these, 159 individuals with both baseline and follow-up were included for analysis. The State Director General of Education approved the ASHFS in 1985 and the Southern Tasmania Health and Medical Research Ethics Committee approved CDAH3 follow-up trial.

1.8 Concluding remarks

This chapter provides an overview of burden of heart failure and the recognition of preclinical stage of heart failure – SBHF. In summary, the findings suggest the following: 1) to reduce the burden of heart failure, a preventive strategy could be targeted to the preclinical SBHF; 2) a variety of risk factors are known to be associated with heart failure. Knowing the relative magnitude of each risk factor and their combined risk can facilitate the identification of highest individuals for further echocardiographic screening; 3) active screening in the community with an effective screening strategy will improve effectiveness of screening; 4) no evidence is available to define the benefit of pharmacological treatment for patients with non-ischemic SBHF.

This thesis aims to evaluate the benefit of cardiac imaging surveillance in the community of non-ischaemic SBHF followed by imaging guided cardio-protective treatment. Findings of this research are to fill the current evidence gaps.

Postscript

The next chapter aimed to perform a systematic review and meta-analysis to identify a series of clinical risk factors and to assess the relative magnitude of common risk factors of incident heart failure.

Other non-imaging tools including biochemical markers, electrocardiogram and hand-held ultrasound devices potentially suitable for screening are also to be summarized in the next chapter.

Chapter 2

Clinical Prediction of Incident Heart Failure Risk

The Systematic Review from this chapter

“Clinical Prediction of Incident Heart Failure Risk: a systematic Review and meta-analysis” was published in

Open Heart 2015;2(1): e000222

Hong Yang, Kazuaki Negishi, Petr Otahal, Thomas H Marwick

Chapter 2. Clinical Prediction of Incident Heart Failure Risk

Introduction

The prediction of incident heart failure using non-imaging markers includes clinical prediction (often risk scores), biochemical markers, electrocardiogram and hand-held ultrasound devices. This chapter will summarize and give an overview of evidence in the literature on these non-imaging tools. The purpose is to seek an initial screening strategy using readily available information to optimize the feasibility and effectiveness of a screening program. A systematic review was performed to evaluate the clinical prediction of incident heart failure. Other non-imaging markers are also summarized in this chapter including biochemical markers, Electrocardiogram and Handheld ultrasound devices.

The available heart failure risk scores were either derived from selected populations or contain biomarkers limiting the use in community setting. The following section aims to perform a systematic review of the common heart failure risk factors from community unselected populational studies. We intended to quantify the relative magnitude of these risk factors and their combined effects. This systematic review was to prepare and exercise the argument about “who to screen” for a community screening and interventional study.

The following text in this section has been published in ***Open Heart Open Heart 2015; 2(1): e000222***

2.1 Clinical Prediction of Incident Heart Failure Risk – A systematic review and Meta-analysis

Abstract

Background. Early treatment may alter progression to overt heart failure (HF) in asymptomatic individuals with stage B heart failure (SBHF). However, the identification of patients with SBHF is difficult. This systematic review sought to examine the strength of association of clinical factors with incident HF, with the intention of facilitating selection for HF screening.

Methods. Electronic databases were systematically searched for studies reporting risk factors for incident HF. Effect sizes; typically hazard ratios (HR) of each risk variable were extracted. Pooled crude and adjusted hazard ratios with 95% confidence intervals (CIs) were computed for each risk variable using a random-effects model weighted by inverse variance.

Results. Twenty-seven clinical factors were identified to be associated with risk of incident HF in 15 observational studies in unselected community populations which followed 456,850 subjects over 4-29 years. The strongest independent associations for incident HF were coronary artery disease (CAD; HR=2.94; 95% CI 1.36-6.33), diabetes mellitus (DM; HR=2.00; 95% CI 1.68-2.38), age (HR [per 10 years] =1.80; 95% CI 1.13-2.87) followed by hypertension (HTN; HR=1.61; 95% CI 1.33-1.96), smoking (HR=1.60; 95% CI 1.45-1.77), male gender (HR=1.52; 95% CI 1.24-1.87) and body mass index (BMI; HR [per 5 kg/m^2] =1.15; 95% CI 1.06-1.25). Atrial fibrillation (HR=1.88; 95% CI 1.60-2.21), left ventricular hypertrophy (HR=2.46; 95% CI 1.71-3.53) and valvular heart disease (HR=1.74; 95% CI 1.07-2.84) were also strongly associated with incident heart failure but were not examined in sufficient papers to provide pooled hazard estimates.

Conclusion. Prediction of incident HF can be calculated from 7 common clinical variables. The risk associated with these may guide strategies for the identification of high-risk people who may benefit from further evaluation and intervention.

2.1.1 Background

What is already known about this subject? A variety of risk factors are known to be associated with heart failure - ranging from social determinants of health, to lifestyle characteristics (smoking, physical inactivity, increased salt intake) and common comorbidities (hypertension, type 2 diabetes mellitus (T2DM), coronary artery disease (CAD), obesity and metabolic syndrome (MS) and precursors of myocardial disease including a history of chemotherapy or a family history of cardiomyopathy.

What does this study add? The relative magnitude of these risk factors, and their combined effects, are not well known. This systematic review sought to examine the strength of association of clinical factors with incident HF, with the intention of creating a practical clinical score to facilitate selection for HF screening. The strongest associations for incident HF (adjusted HR ≥2) were coronary artery disease (CAD; HR=2.94; 95%CI 1.36-6.33) and diabetes mellitus (DM; HR = 2.00; 95%CI 1.68-2.38). Adjusted HR ≥1 were age (HR [per 10 years] = 1.80; 95%CI 1.13-2.87), hypertension (HTN; HR = 1.61; 95%CI 1.33-1.96), smoking (HR = 1.60; 95%CI 1.45-1.77), male gender (HR = 1.42; 1.27-1.59) and body mass index (BMI; HR [per 5 kg/m^2] = 1.15; 95% CI 1.06-1.25). Thus, incident HF could be predicted from 7 common clinical variables.

How might this impact on clinical practice? The early detection of asymptomatic patients with LV dysfunction is now possible with a variety of sensitive biochemical and imaging techniques, and should lead to the use of cardioprotective strategies to prevent progression of disease. The estimation of HF risk is a critical step in appropriate selection of patients for imaging.

The incidence and prevalence of heart failure (HF) are growing and assuming epidemic proportions, affecting an estimated 23 million people worldwide [21]. In the United States, 5 million people suffer from HF with a rate of 550,000 new cases diagnosed each year [25]. HF is predominantly a problem of old age, the most frequent cause of hospitalization in the elderly and a major burden on the community due to the cost of care and poor quality of life. The total direct and indirect cost of heart failure in US exceeds $30 billion [24], where it accounts for 12-15 million office visits and 6.5 million hospital days each year [25].

The morbidity and cost of late-stage HF may be delayed or even prevented by pharmacologic interventions, once evidence of structural heart disease (stage B HF) has been defined[37-42]. Subclinical cardiac impairment is most readily identifiable in patients with prior myocardial infarction. Identification of stage B HF in the approximately 50% of HF patients who are non-ischaemic might be possible with echocardiographic or biochemical screening [44], but this would be most feasible if there was a means of identifying risk on clinical grounds. Various risk factors have been associated with HF, ranging from lifestyle characteristics such as smoking, physical inactivity, increased salt intake and lower socioeconomic status to common comorbidities including hypertension, type 2 diabetes mellitus (T2DM), coronary artery disease (CAD), obesity and metabolic syndrome (MS). Risk factors also include a history of chemotherapy or a family history of cardiomyopathy [98,99]. We undertook a systematic review and meta-analysis of studies reporting risk factors relating to incident heart failure in unselected community-based populations.

2.1.2 Aims and Hypothesis

The goal of this was to identify a series of clinical markers which could be used to identify subjects from a community-based population in whom further evaluation and intervention might be warranted.

2.1.3 Methods

Search Strategy. The research strategy, study selection and analysis method used in the study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA)[100]. Electronic databases (MEDLINE, EMBASE) were systematically searched for published studies reporting risk factors related to incident HF. Search key terms were: "incident heart failure" and "risk factors", "risk assessment", "risk impact", "risk prediction", "risk score", “risk prevention”. To ensure the identification of all relevant articles and publications, the reference lists of these articles were also reviewed to identify additional studies. The last search was performed on 7 October 2013.

Study inclusion. From these lists, studies were included if they met each of the following criteria: (1) studies of a full-length publication in a peer-reviewed English language journal; (2) studies done in human adults >18 years of age; (3) studies done in an unselected community population; (4) studies reporting risk factors relating to incident heart failure; (5) studies using Cox Proportional hazard models reporting risk effect sizes in Hazard Ratio (HR) with 95% confidence intervals (CIs) and/or associated p value. This review incorporated mainly observational cohort studies.

Outcomes. The primary outcome of interest was incident HF. The criteria for identification of incident HF were described as one or more of the following: (i) medical diagnosis from physician's records; (ii) evidence of treatment for HF (i.e. diuretics and either digitalis or a vasodilator); (iii) hospital or nursing home stays in which the participant had a discharge diagnosis with a code of International Statistical Classification of Diseases and related health problems (ICD-9 code) of 428.0 to 428.9; (iv) death certificate report in which the underlying cause of death was recorded using an ICD-9 code of 428.0 to 428.9.

Data extraction. Data was extracted independently by reviewers (HY, KN and PO). All discrepancies were reviewed and resolved by consensus. For the systematic review, the following data concerning the individual study populations was extracted: demographic and clinical characteristics and associated risk prevalence at baseline; study design; years of follow-up; statistical models; statistic models; risk effect sizes and their associated 95% confidence intervals (CIs) with p values; covariates included in the risk assessment models in relation to outcome. In situations in which multiple articles were published from a single cohort, data were included only if different risk variables were analysed and reported.

Statistical analysis. Reported risk effect sizes and the statistical models used in each study were reviewed. Crude measures of effect with 95% CIs were extracted for each risk variable. Multiple within-study effects stratified in subgroups were combined by weighting each group by its number of participants. Study risk estimates reported per categorical change were re-calculated as continuous variables for BMI [101]. Risk estimates from the majority of studies were estimated using Cox proportional hazard models and were pooled as Hazard Ratios (although some incorrectly labelled these as Relative Risk/Rate) [102,103]. Risk estimates reported as "Relative Risk" using Mantel-Haenszel [104] or linear regression model [105] or Odds Ratio using logistic regression model[106] were excluded for further analysis. Consequently, pooled risk estimates were all from studies using Cox proportional hazard models and were suitable for providing summary risk estimates. Both unadjusted and maximally adjusted risk effects were pooled using random effect models weighted by inverse variance [107]. Further a subset of studies reporting seven mutually adjusted risk effects (age, male gender, BMI, smoking, HTN, DM, CAD) were also pooled. When confidence intervals were not reported, their associated p values were used to estimate variance of the risk estimate [108].

The Cochrane Q statistic and I^2 values index were used to assess the degree of heterogeneity across studies. Funnel plots were constructed and Egger's test was used to assess potential publication bias. Duval and Tweedie's Trim and Fill method was used to assess the potential effects of publication bias on risk estimates. Meta-regression was also performed for each risk factor to examine possible study factors associated with heterogeneity. The assessment of study quality was performed using the Newcastle-Ottawa Scale (NOS) for non-randomized studies in meta-analyses [109]. Statistical analysis was performed using statistics package R version. 3.1.1.

2.1.4 Results

Study selection. The process of article selection based on PRISMA guidelines is presented in Figure 2.6.

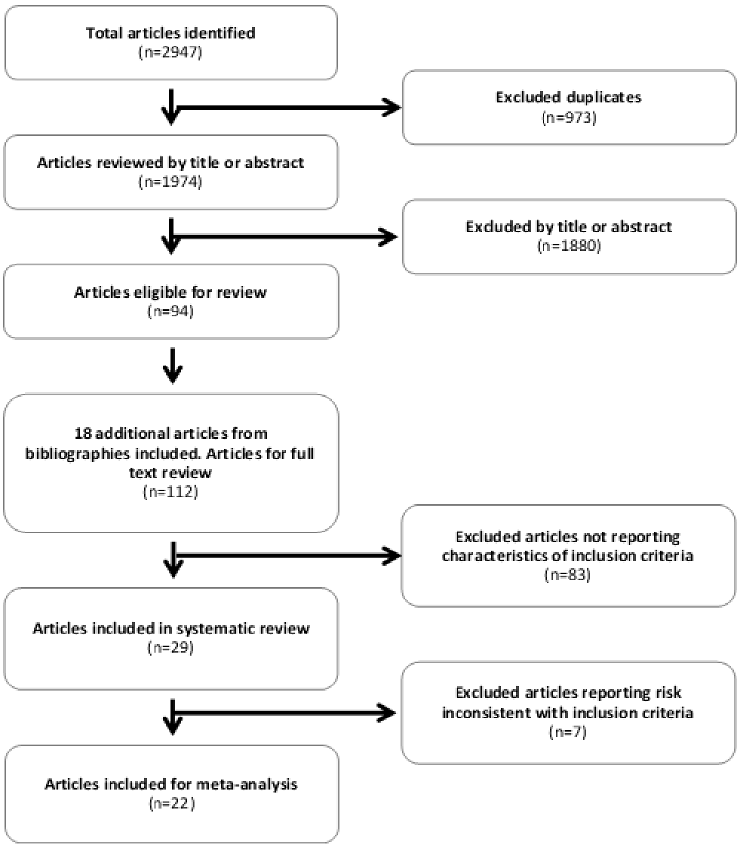


Figure 2.6 The process of article selection based on PRISMA guidelines

After exclusion of duplicates, the initial search revealed a total of 1974 original articles published from 1967-2013. After exclusion of inappropriate papers, or studies without relevant risk analysis, there were 15 studies eligible for inclusion, from which 4 studies had more than one eligible article either from the same data set or from a pilot study set. Therefore, a total of 20 articles were systematically reviewed and eligible for quantitative synthesis (Figure 2.6)[60,78-80,102-104,108,110-121]. Risk estimates from two articles [80,110] were not included in the meta-analysis since they duplicated estimates from the same cohort, and estimates from Kalogeropoulos [104] and Mujib [108] were only included where they were absent from the corresponding articles on the same cohorts; Butler [79] and Gottdiener [103], respectively. The included articles were published between 1993 and 2013.

Baseline characteristics. The baseline demographic characteristics of included studies (15 prospective cohort studies) are summarized in Table 2.2.

The geographic distribution of the studies was predominantly in North America and Europe (11 studies in US, 4 in Europe). There were a total of 456,850 subjects – the reported mean age of participants was 24-81 years (weighted mean 42±13 years), the proportion of male participants ranged from 32%-100% (weighted mean 49±9%), and the majority of the participants were Caucasian 39%-100% (weighted mean 64±6%). Over an average follow-up time of 4-29 years, there were 11467 incident HF cases, giving an average cumulative incident HF rate of 0.97±0.11% (Table 2.2).

Table 2.2 Baseline population demographic characteristics and risk prevalence

	Author(s)	**Publish** (year)	**Trial** (study name)	**Total** (n)	**Follow Up** (year)	**Incident HF** (n)	**Cumu * Incidence**	**Age** (years)	**% male**	**Risk ratio**	**Stats Model used**	**% Smoke**	**BMI**	**% DM**	**% CAD**	**% LVH**	**% HTN**	**% VHD**
1	Ho KK et al [110] Kannel et al[80] Ho J et al[60]	1993 1999 2013	Framingham and offspring (US)	9405 ǂ 15267 pe* ǂ 6340	40ǂ 38ǂ 8	652ǂ 486ǂ 512	 8.1%	 60±12	 46%	RR OR HR	CPH PLR CPH	 22%	 27±4	 7%	 8%	 8%	 46%	 1%
2	Butler et al[79] Kalogeropoulos et al[104]	2008 2009	Health ABC study (US)	2934	7	258	8.8%	74±2.9	48%	HR RR	CPH MH	56%	27.3±4.8	15%	17%	12%	43%	
3	He et al[102]	2001	NHANES (US)	13643	19	1382	10.1%	50±15	41%	RR §	CPH	35%	25.6±5	4%	5%		28%	5%
4	Agarwal et al[78]	2012	ARIC (US)	13555	16	1487	11.0%	54±5.8	45%	HR	CPH	25%	27.6±5.2	10%	4%	2%		1%
5	Goyal et al[111]	2010	Million P-Yr* (US)	359947	5	4001	1.1%	38±14	47%	HR	CPH			3%	1%		12%	1%
6	Bahrami et al[112] Bahrami et al[113]	2008 2008	MESA (US)	6814	4	79	1.2%	65±0.7	47%	HR	CPH	49%	28.4±0.1	14%		10%	48%	
7	Gottdiener et al[103] Mujib et al [108]	2000 2010	Cardio Vascular Health (US)	5625	12	597	10.6%	73±4.5	42%	RR HR	CPH CPH	54%		17%			58%	
8	Chen et al[114]	1999	EPESE (US)	1749	8	173	9.9%	74±6.8	41%	HR	CPH	78%		11%			54%	
9	Bibbins-D et al[115]	2009	CARDIA (US)	5115	20	27	0.5%	24±3.5	45%	HR	CPH	31%	24.5±4.8	2%		6%	3%	
10	Ingelsson et al[116]	2005	ULSAM (Sweden)	2321	29	259	11.2%	50±0.0	100%	HR	CPH	51%	25±3.2	6%	0%	2%	43%	
11	Wang et al[117]	2010	Kuopio (Finland)	1032	21	303	29.4%	69±2.8	38%	HR	CPH	29%	27.2±4.0	17%	7%	31%	26%	
12	Aronow et al[118]	1999	Mt Sinai (US)	2902	4	794	27.4%	81±8.0	32%	HR	CPH			25%	44%		46%	
13	Smith et al[119]	2010	MDCS (Sweden)	5187	14	112	2.2%	58±5.9	41%	HR	CPH	27%	25.7±3.9	8%	2%		17%	
14	Kenchaiah et al[120]	2009	Physician's heart (US)	21094	21	1109	5.3%	53±9.4	100%	HR	CPH	48%	24.8±1.4	3%	9%		24%	
15	Brouwers et al[121]	2013	Prevend (Netherlands)	8592	12	374	4.4%	49±12	50%	HR	CPH	38%	26±4.0	4%	6%		32%	
	Sum	1993 - 2013	15 studies	456850	198	11467												
	Mean (Weighted)			30457	7	3323	0.97%	42	49%			39%	26	4%	2.23%	6%	16%	1%
	SD (Weighted)				1.0	811	0.11%	12.6	9%			2.70%	3	1%	0.23%	1%	3%	0.2%
	Maximum			359947	29	4001	29.36%	81	100%			78%	28	25%	44%	31%	58%	5%
	Minimum			1032	4	27	0.53%	24	32%			22%	25	2%	0.3%	1.5%	3.0%	0.5%

* pe (person exam); Cum incidence (Cumulative incident rate); P-Yr (person year); ǂ duplicated counts from a single study, not included in total and cumulated incidence; BMI (Body mass Index); DM (Diabetes mellitus); CAD (Coronary Artery Disease); LVH (Left Ventricular Hypertrophy); HTN (Hypertension); VHD (Valvular Heart Disease); RR (Relative Risk); OR (Odds Ratio); HR Hazard Ratio); CPH (Cox Proportional Hazard); PLR (Pooled Logistic Regression); MH (Mantal Haenszel); § RR (Risk Ratio);

FHS (Framingham Heart Study); HABC (Health Aging and Body Composite Study); NHANES (National Health Nutrition Examination Survey); ARIC (The Atherosclerosis Risk in Communities); Million P-Y (One Million Person-Year study); MESA (Multi-Ethnic Study of Atherosclerosis); CVH (Cardio Vascular Health study); EPESE (Established Population for Epidemiologic Studies of the Elderly program); CARDIA (Coronary Artery Risk Development in Young Adults); ULSAM (Uppsala Longitudinal Study of Adult men); Kuopio (Kuopio Finland study); Mt Sinai (Study at Mt Sinai); MDCS (the Malmo diet and Cancer Study in Swedish people); Physician Heart (the Physician heart study); Prevend (Prevention of Renal and Vascular End-stage Disease)

The detailed baseline prevalence of cardiovascular and non-cardiovascular comorbidities is summarized in Table appendix 2.5 and Table appendix 2.6. The BMI was 25-28 kg/m^2 (weighted mean 26±3kg/m^2). The prevalence of DM varied from 2%-25% (weighted mean 4±1%), CAD varied from 0.3-44% (weighted mean 2.2±0.2%), HTN 3%-58% (weighted mean 16±2%) and left ventricular hypertrophy (LVH) 1.5-31% (weighted mean 6±1%). In the study populations, 22%-78% were either current or past smokers.

Clinical factors associated with incident HF. Twenty-seven variables were reported to be associated with incident HF, including twenty clinical variables, six biomarkers and one echocardiographic marker. These variables were age, male gender, black race, family history of cardiac disease, excessive use of alcohol, smoking, physically inactive, obesity, education level, DM, CAD, LVH by ECG, HTN, chronic obstructive pulmonary disease (COPD), valvular heart disease (VHD), chronic kidney disease (CKD), stroke, resting heart rate, atrial fibrillation (AF), abnormal ECG which includes bundle brunch block, ST-T and QRS changes, and echocardiographic left ventricular ejection fraction (LVEF). Biomarkers were fasting glucose, C - reactive protein (CRP), creatinine, albumin, dyslipidaemia and NT-proBNP.

Crude and adjusted risk ratios were extracted. The reporting details of each risk variable and overall reporting frequency are summarized in Table appendix 2.7. We selected variables only if they were reported in four or more of the included studies for quantitative synthesis. Thirteen variables meet this requirement. We excluded abnormal ECG due to heterogeneous criteria based on the presence of QRS changes [78]; ST-T changes [103] and bundle bunch block [60]. We also excluded dyslipidaemia and fasting glucose, due to inconsistency in categorical [102,113,117,121] as well as continuous cut-offs of these two biomarkers [60,78,79,116] in risk calculation between studies. Therefore, a total of 11 risk variables (age, male gender, race black, obesity, and smoking, DM, CAD, HTN, LVH, VHD and AF) were selected for further synthesis. Pooled unadjusted and adjusted HRs with 95% CIs are listed in Table 2.3**.**

The details of other factors used in multivariate models of included studies are summarized in Table appendix 2.8.

Strength of independent association with incident HF. Further subset meta-analyses were conducted from 6 studies [60,102,103,116,119,121], where each of 7 risk variables was mutually adjusted in models within each study. The strength of independent association for incident HF was highest for CAD (2.94 [1.36-6.33]) followed by DM (2.00 [1.68-2.38]) and age (per 10 years increase) (1.8 [1.13-2.87]) (Table 2.4).

Publication bias, sensitivity and study quality. Egger's test for pooled adjusted risk indicated significant bias for the estimates of BMI, male gender, and atrial fibrillation (Table 2.3B), and BMI for mutually adjusted risk estimates (Table 2.4). No publication bias was detected for crude estimates (Table 2.3A). Duval and Tweedie's trim and fill results are presented for all risk estimates where at least three studies were pooled. The NOS scale [109] for cohort studies is summarized in Table appendix 2.9; most studies were of high quality.

Exploration of study heterogeneity. Meta-regression was performed for each of the seven risk factors in the mutually adjusted models; the following study factors were examined: follow-up time, cumulative incidence, mean age, male proportion, and smoking proportion, mean BMI, DM proportion, HTN proportion, VHD proportion, CAD proportion, study quality. Even though the estimates from these seven studies were adjusted for smoking, the pooled risk effect of DM increases by approximately 10% for each 10% increase in the proportion of smokers in a study, implying some interaction between these risks. Likewise, the pooled risk effect of male sex increases by 38% for each 10% increase in the proportion of subjects with diabetes in a study.

Table 2.3 Pooled risk estimates of risk variables (Unadjusted and adjusted)

A) Unadjusted

	Pooled HR	95% CI	I^2	Study (n)	Q-Chi2	Q-p value	Eggers test	Trim-fill HR[95%CI]
BMI(5kg/m2)	1.54	1.21 - 1.95	96.5	4	86.2	<0.001	0.553	1.28 [1.03-1.59]
Sex (Male)	1.51	1.07 - 2.12	52.5	3	4.2	0.122	0.916	1.51 [1.07-2.12]
Smoker (yes)	1.82	1.49 - 2.23	48.0	4	5.8	0.123	0.505	2.03 [1.65-2.49]
Race (Black)	1.78	1.60 - 1.98		1				
Age (10yr)	2.29	2.09 - 2.51	57.2	4	7.0	0.072	0.842	2.29 [2.09-2.51]
HTN (yes)	3.49	1.25 - 9.74	98.5	4	195.9	<0.001	0.111	8.35 [3.16-22.09]
Diabetes (yes)	3.27	2.27 - 4.72	93.3	6	74.6	<0.001	0.278	4.49 [3.15-6.39]
VHD (yes)	3.92	1.85 - 8.31	96.2	2	26.2	<0.001	*	
CAD (yes)	5.07	2.47 - 10.40	97.5	4	120.5	<0.001	0.496	9.63 [4.64-20.00]
LVH (yes)	4.40	2.25 - 8.58	87.2	5	31.3	<0.001	0.527	3.29 [1.63-6.64]
AF (yes)	13.77	11.79 - 16.08		1				

B) Adjusted

	Pooled HR	95% CI	I^2	Study (n)	Q-Chi2	Q-p value	Eggers test	Trim-fill HR[95%CI]
BMI(5kg/m2)	1.21	1.10 - 1.33	94.1	9	134.8	<0.001	0.062	1.05 [0.96-1.16]
Sex (Male)	1.51	1.32 - 1.72	58.1	8	16.7	0.019	0.020	1.32 [1.14-1.53]
Smoker (yes)	1.65	1.45 - 1.88	43.3	8	12.3	0.090	0.201	1.56 [1.34-1.82]
Race (Black)	0.96	0.75 - 1.23	73.3	4	11.3	0.010	0.825	0.91 [0.72-1.16]
Age (10yr)	1.70	1.33 - 2.16	99.1	9	848.2	<0.001	0.949	1.70 [1.33-2.16]
HTN (yes)	1.79	1.41 - 2.27	91.9	11	123.7	<0.001	0.533	2.55 [1.92-3.37]
Diabetes (yes)	1.94	1.71 - 2.19	56.4	11	23.0	0.011	0.400	1.94 [1.71-2.19]
VHD (yes)	1.74	1.07 - 2.84	92.9	3	28.0	<0.001	0.150	1.74 [1.07-2.84]
CAD (yes)	2.90	1.85 - 4.54	97.2	9	285.5	<0.001	0.987	2.90 [1.85-4.54]
LVH (yes)	2.46	1.71 - 3.53	74.1	6	19.3	0.002	0.431	2.17 [1.47-3.19]
AF (yes)	1.88	1.60 - 2.21	16.2	4	3.6	0.310	0.020	1.99 [1.66-2.39]

* Eggers test only used if number of studies was three or greater.

Table 2.4 Pooled hazard risk estimates for mutually adjusted risk variables

	Pooled HR	**95% CI**	**I^2**	**Study (n)***	**Q-Chi2**	**Q-p value**	**Eggers test**	**Trim-fill HR[95%CI]**
BMI(5kg/m2)	1.15	1.06 - 1.25	89.8	5	39.34	<0.001	0.039	1.06 [0.96-1.16]
Male Gender	1.52	1.24 - 1.87	71.5	5	14.05	0.007	0.107	1.27 [1.03-1.56]
Smoker (yes)	1.60	1.45 - 1.77	0.0	5	2.69	0.611	0.783	1.60 [1.45-1.77]
HTN (yes)	1.61	1.33 - 1.96	64.1	5	11.14	0.025	0.358	1.41 [1.15-1.73]
Age (10yrs)	1.80	1.13 - 2.87	99.1	4	331.4	<0.001	0.64	2.41 [1.49-3.91]
DM (yes)	2.00	1.68 - 2.38	50.6	6	10.12	0.072	0.841	2.00 [1.68-2.38]
CAD (yes)	2.94	1.36 - 6.33	97.7	6	212.6	<0.001	0.583	6.71 [2.69-16.74]

***** Number of studies included in estimates for each listed risk factor

2.1.5 Discussion

The findings of this systematic review demonstrated 11 common cardiovascular and non-cardiovascular risks associated with incident HF. Results from meta-analysis revealed the independent risk associated with the 7 most common comorbidities. Knowledge of the relative effect sizes may facilitate the process of risk assessment in a community-based population. The factors most strongly independently associated with incident HF were CAD (2.94 [1.36-6.33]) followed by DM (2.00 [1.68-2.38]).

Calculation of HF risk. Although the role of heart failure risk factors has been documented in numerous previous publications, the reported level of risk has been heterogeneous, so the relative contribution of each factor to the development of heart failure remains controversial. To date, three population-based studies have sought to integrate risk factors into single estimate of HF risk [78-80]. Of these, the ARIC HF risk score is a well-validated parsimonious score, whereas concern has been expressed regarding the selection of patients into the Framingham Heart Failure Risk Score (which is much influenced by ischaemic aetiology), and the Health ABC Heart Failure Score requires blood testing that may not be accessible at community screening.

It is paradoxical that while the performance of an echocardiogram is considered appropriate in patients with symptomatic HF, its use in the preclinical stage is considered inappropriate [122]. Perhaps this is the reason that screening for HF has not been widely applied, even in at-risk patients such as those with diabetes mellitus, hypertension and CAD, despite the wide availability of echocardiographic assessment of systolic and diastolic dysfunction. Moreover, LV assessment using 2D imaging may be hard to reproduce, and although there have been initial reports of both in community studies [123], the place of both in community screening is undefined. In any case, some clinical definition of risk would still be required.

Heart failure screening. Stage B HF (SBHF) lies between overt HF (stages C and D) and patients with heart failure risk factors (stage A). These asymptomatic patients have evidence of LV damage, which may be detected as disturbances of LV structure or function, which predispose toward the development of HF [124]. SBHF is relatively easy to identify in patients with previous myocardial infarction and regional dysfunction, or with reduced ejection fraction. However, nearly 50% of HF is of non-ischaemic origin [44], and in this circumstance, the identification of SBHF may be difficult in the absence of LVH.

Although HF may be prevented by control of HF risk factors, early detection of LV dysfunction may permit the institution of measures that prevent progression of the problem[39,125,126]. Screening for SBHF is supported by previous studies of subclinical LV systolic and diastolic dysfunction. The prevalence of asymptomatic EF <50% is 7.2% in those aged 60-69 years and doubles to 14.3% in those aged >80 years [51]. The prevalence of diastolic dysfunction varies with grade among patient with different risk groups. In older (>65 years) patients with a diagnosis of hypertension or coronary disease, the prevalence of mild diastolic dysfunction is 36%, moderate or severe is 16% [56]. Abnormal myocardial function can be documented in 20-30% of patients with obesity and diabetes [58,59].

The application of any screening test is most effective when the condition is of at least moderate prevalence in the population under study. For example, focusing the screening effort on those with non-ischaemic risk factors for HF (diabetes, hypertension, overweight, metabolic syndrome, cardiotoxic chemotherapy, familial cardiomyopathy) would permit restriction of screening tests to the group most likely to have a problem. Nonetheless, these HF risks are highly prevalent in general population and their relative and additive importance are not well known.

The consistency of association of various risk factors with heart failure supports the concept that heart failure is predictable in many patients. The development of this simple risk calculation strategy derived from this study could be used to focus resources (e.g. open access echocardiography) on at-risk non-ischaemic patients. However, the predictive value of the risk calculation, the benefit of imaging surveillance and the cost-effectiveness of screening of stage A HF in the community will need to be validated prospectively. We are undertaking this at present in a population-based study (http://www.anzctr.org.au/; ACTRN12614000080628)

2.1.6 Study Limitations

Like all meta-analyses, this work is limited by variations in the original studies, although all involved at-risk individuals. Likewise, the constituent observational studies may be limited by biases in the recruitment process. The high levels of I^2

attest to substantial heterogeneity between studies. The original intention of the analysis was to develop a risk score using the available clinical variables. This was limited by the heterogeneity in the studies; particularly in the various cohorts used in each study and in the variables used for adjustment. Without access to individual-level data, we can only propose the combined risk measures derived from this study be used as a marker of the magnitude rather than as exact risk estimates. Furthermore, our primary interest was to identify and quantify the potential HF risks in non-ischemic HF. While CAD is ubiquitous in these, the proportion with CAD is low (weighted average 2.2%, Table 1). Moreover, the benefit of a meta-regression is that we were able to address the role of other factors independent of CAD. Finally, this systematic review was not registered prospectively

2.1.7 Conclusion

This systematic review and meta-analysis of 456,850 subjects shows that CAD, diabetes, age, hypertension, smoking, male gender and increased BMI are consistently and independently associated with a higher risk of incident HF. Atrial fibrillation, left ventricular hypertrophy and valve heart disease are also strongly associated with incident HF. The estimation of HF risk may become useful in selection of asymptomatic patients for imaging as sensitive, new imaging and biochemical techniques for identification of LV dysfunction become more widely available.

Appendix Tables and figures

Table appendix 2.5 -Baseline characteristics of included studies (demographic)

	Study	**Publish** (year)	**Trial** (study name)	**Data Collection** (year)	**Total** (n)	**Follow-Up** (year)	**HF develop** (n)	**Incident Rate** (1000 p-yr*)	**Cumulative Incident rate** (%)	**Age** (±SD)	**Gender** (%male)
1	Ho KK et al [110]	1993	Framingham and offspring (US)	1948-1988	9405 ǂ	40ǂ	652ǂ	1.85			
	Kannel et al[80]	1999			15267 pe*ǂ	38ǂ	486ǂ				
	Ho J et al[60]	2013		1981-2008	6340	8	512	5	8.1%	60±12	46%
2	Butler et al[79] Kalogeropoulos et al[104]	2008 2009	Health ABC study (US)	1997-2004	2934	7	258	13.6	8.8%	74±2.9	48%
3	He et al[102]	2001	NHANES (US)	1971-1992	13643	19	1382		10.1%	50±15	41%
4	Agarwal et al[78]	2012	ARIC (US)	1987-2005	13555	16	1487		11.0%	54±5.8	45%
5	Goyal et al[111]	2010	Million P-Yr *(US)	2000-2005	359947	5	4001	3.96	1.1%	38±14	47%
6	Bahrami et al[112] Bahrami et al[113]	2008 2008	MESA (US)	2000-2006	6814	4	79	3.1	1.2%	65±0.7	47%
7	Gottdiener et al[103] Mujib et al [108]	2000 2010	Cardio Vascular Health (US)	1989-1996	5625	12	597	19.3	10.6%	73±4.5	42%
8	Chen et al[114]	1999	EPESE (US)	1982-1992	1749	8	173	12.5	9.9%	74±6.8	41%
9	Bibbins-Domingo et al[115]	2009	CARDIA (US)	1985-2006	5115	20	27		0.5%	24±3.5	45%
10	Ingelsson et al[116]	2005	ULSAM (Sweden)	1970-2001	2321	29	259	4.5	11.2%	50±0.0	100%
11	Wang et al[117]	2010	Kuopio (Finland)	1986-2006	1032	21	303		29.4%	69±2.8	38%
12	Aronow et al[118]	1999	Mt Sinai (US)	N/A	2902	4	794		27.4%	81±8.0	32%
13	Smith et al[119]	2010	MDCS (Sweden)	1991-	5187	14	112		2.2%	58±5.9	41%
14	Kenchaiah et al[120]	2009	Physician's heart (US)	1982-2007	21094	21	1109	2.57	5.3%	53±9.4	100%
15	Brouwers et al[121]	2013	Prevend (Netherlands)	1997-2010	8592	12	374		4.4%	49±12	50%
	Sum	1993-2013	15 studies	1967-2007	456850	198	11467				
	Mean (Weighted)				30457	7	3323	3.75	0.97%	42	49%
	SD (Weighted)					1.0	811	1.07	0.11%	12.6	9%
	Maximum				359947	29	4001	19.3	29.36%	81	100%
	Minimum				1032	4	27	2.57	0.53%	24	32%

*pe (person exam); p-yr (person year); ǂ duplicated counts from a single study, not included in counts for total and cumulated incidence.
FHS (Framingham Heart Study); HABC (Health Aging and Body Composite Study); NHANES (National Health Nutrition Examination Survey); ARIC (The Atherosclerosis Risk in Communities); Million P-Y (One Million Person-Year study); MESA (Multi-Ethnic Study of Atherosclerosis); CVH (Cardio Vascular Health study); EPESE (Established Population for Epidemiologic Studies of the Elderly program); CARDIA (Coronary Artery Risk Development in Young Adults); ULSAM (Uppsala Longitudinal Study of Adult men); Kuopio (Kuopio Finland study); Mt Sinai (Study at Mt Sinai); MDCS (the Malmo diet and Cancer Study in Swedish people); Physician Heart (the Physician heart study); Prevend (Prevention of Renal and Vascular End-stage Disease)

Table appendix 2.6 -Baseline characteristics of included studies (Risk prevalence)

Author(s)	% White	% >Hi/Sc*	% F/Hx*	% Smoke	% Alcohol	BMI (mean)	SBP (mean)	DBP (mean)	% Inactive	% DM	% CAD	% LVH	% HTN	% VHD	% Stroke or TIA	% Abn ECG	Heart rate (mean)	% COPD	% AF	% CKD	Total CHOL
Ho KK et al ; [110]																					
Kannel et al;[80]																					
Ho J et al[60]	100%			22%		27±4	132	77±11		7%	8%	8%	46%	1%	3%	3%	65		2%		213
Butler et al; [79] Kalogeropoulos et al[104]	59%	89%		56%		27±5	136	71±12		15%	17%	12%	43%		7%		65				203
He et al[102]	85%	56%		35%	25%	26±5	134		44%	4%	5%		28%	5%							222
Agarwal et [78]al[78]	74%			25%		28±5	120			10%	4%	2%		1%		3%	67	8%			
Goyal et al[111]										3%	1%		12%	1%					0%		
Bahrami et al[112] Bahrami et al[113]	39%			49%		28±0.0	127	72±0.2		14%		10%	48%								194
Gottdiener et al[103] Mujib et al [108]	85%	71%		54%			136	71±11		17%			58%		5%	15%		25%	2%		211.9
Chen et al[114]	80%	48%		78%						11%			54%		4%						
Bibbins-D et al[115]	48%	60%	12%	31%	12%	25±5	110	69±9		2%		6%	3%							4%	
Ingelsson et al[116]				51%		25±3				6%	0%	2%	43%								
Wang et al[117]				29%	30%	27±4	157	82±14	25%	17%	7%	31%	26%								254
Aronow et al[118]	67%									25%	44%		46%								
Smith et al[119]				27%		26±4	141	87±9		8%	2%		17%						1%		
Kenchaiah et al et al[120]				48%	25%	25±1	126	79±7	14%	3%	9%		24%								
Brouwers et al[121]	95%			38%		26±4	128	74±10		4%	6%		32%				69		1%	6%	199
Sum																					
Mean (Weighted)	64%			39%		26	128	76	25.5%	4%	2.23%	6%	16%	1%	5%	5.8%	67	13.1%	0.4%	5.2%	210
SD (Weighted)	5.8%			2.70%		3	16	8	8.1%	1%	0.23%	1%	3%	0.2%	0.6%	1.4%	10	0.9%	0.1%	1.9%	20
Maximum	100%	89%	12%	78%	30%	28	157	87	44%	25%	44%	31%	58%	5%	7%	15%	69	25%	2%	6%	254
Minimum	39%	48%	12%	22%	12%	25	110	69	14%	2%	0.3%	1.5%	3.0%	0.5%	2.7%	2.7%	65	8.4%	0.3%	3.5%	194

*Hi/Sc (high school); F/Hx (family history of cardiac disease); BMI (Body Mass Index); DM (Diabetes Mellitus); CAD (Coronary Artery Disease); LVH (Left Ventricular Hypertrophy); HTN (Hypertension); VHD (Valvular Heart Disease); TIA (Transient Ischaemic Attack); COPD (Chronic Obstructive Pulmonary Disease); AF (Atrial Fibrillation); CKD (Chronic Kidney Disease); CHOL (cholesterol)

Table appendix 2.7 -Heterogeneity of risk variables reported in studies

Variables	Frequency (n)	(%)	FHS	Health ABC	NHANES	ARIC	Million P-Y	MESA	CVH	EPESE	CARDIA	ULSAM	Kuopio	Mt Sinai	MDCS	Physician Heart	PREVEND
Hypertension	14	93%	+	+	+	+	+	+	+	+	+	+	+	+	+		+
Diabetes	13	87%	+	+	+	+	+	+	+	+	+	+		+	+		+
Age	11	73%	+	+		+	+	+	+	+	+			+	+		+
Male Gender	11	73%	+		+	+	+	+	+	+	+			+	+		+
Obesity	10	67%	+		+	+				+	+	+	+		+	+	+
Smoking	10	67%	+	+	+	+		+	+		+	+			+		+
CAD	10	67%	+	+	+	+	+		+			+		+	+		+
Dyslipidaemia	8	53%	+		+	+		+			+	+	+				+
LVH	7	47%	+	+		+		+	+		+	+					
Black Race	6	40%			+	+		+	+		+			+			
Fasting Glucose	5	33%		+		+			+				+				+
Valvular Disease	4	27%	+		+	+	+										
Atrial Fibrillation	4	27%	+				+		+								+
Abnormal ECG	3	20%	+			+			+								
Heart Rate	3	20%	+	+		+											
Excessive Alcohol	3	20%			+						+						
CKD	3	20%		+							+						+
NT-proBNP	3	20%				+									+		+
C-Reactive Protein	3	20%				+			+								+
Albumin	3	20%		+		+			+								
Creatinine	3	20%		+		+			+								
Stroke	2	13%							+						+		
Family History	2	13%									+						
Education	2	13%			+						+						
COPD	2	13%				+			+								
LVEF (echo)	2	13%							+		+						
Physical Inactive	1	7%			+												

CAD (Coronary Artery Disease); LVH (Left Ventricular Hypertrophy); AF (Atrial Fibrillation); VHD (Valvular Heart Disease); COPD (Chronic Obstructive Pulmonary Disease); CKD (Chronic Kidney Disease)
FHS (Framingham Heart Study); HABC (Health Aging and Body Composite Study); NHANES (National Health Nutrition Examination Survey); ARIC (The Atherosclerosis Risk in Communities); Million P-Y (One Million Person-Year study); MESA (Multi-Ethnic Study of Atherosclerosis); CVH (Cardio Vascular Health study); EPESE (Established Population for Epidemiologic Studies of the Elderly program); CARDIA (Coronary Artery Risk Development in Young Adults); ULSAM (Uppsala Longitudinal Study of Adult men); Kuopio (Kuopio Finland study); Mt Sinai (Study at Mt Sinai); MDCS (the Malmo diet and Cancer Study in Swedish people); Physician Heart (the Physician heart study); Prevend (Prevention of Renal and Vascular End-stage Disease)

Table appendix 2.8 -Heterogeneity of risk variables used for adjusted analysis

	Author	**Study** (Trial)	**Risk ratio**	**Stats Model used**	**Age**	**Gender**	**Smoking**	**BMI**	**DM**	**CAD**	**LVH**	**HTN**	**VHD**	**HR**	**AF**	
1	Ho KK[110]	FHS	RR	CPH	+											
	Kannel[80]	FHS	OR	PLR	+	+	+	+	+	+	+	+	+	+		
	Ho J #[60]	FHS	HR	CPH	+	+	+	+	+	+	+	+	+	+	+	LBBB; HDL; MI
2	Butler[79]	Health ABC	HR	CPH	+		+		+	+	+	+		+		creatinine
	Kalogeropoulos[104]	Health ABC	RR	MH			+		+	+	+	+		+		race
3	He#[102]	NHANES	RR	CPH	+		+	+	+	+		+	+			education, alcohol, low physical activity, cholesterol,
4	Agarwal[78]	ARIC	HR	CPH	+	+										
5	Goyal[111]	Million P-Y	HR	CPH	+	+			+	+		+	+		+	
6	Bahrami[112]	MESA	HR	CPH	+	+	+	+	+		+	+				
7	Gottdiener#[103]	CVH	RR	CPH	+	+		+	+	+	+	+				
	Mujib[108]	CVH	HR	CPH	+	+	+		+	+	+	+			+	race, stroke, COPD and peripheral arterial dis
8	Chen YT[114]	EPESE	HR	CPH	+	+		+	+	+		+				
9	Bibbins-D[115]	CARDIA	HR	CPH				+				+				Cholesterol, CKD
10	Ingelsson#[116]	ULSAM	HR	CPH			+	+	+	+	+	+				cholesterol
11	Wang J[117]	Kuopio	HR	CPH	+	+	+		+			+				low physical activity, alcohol cholesterol
12	Aronow[118]	Mt Sinai	HR	CPH	+	+			+	+		+				
13	Smith JG#[119]	MDCS	HR	CPH	+	+	+	+	+	+		+				cholesterol, BNP, CRP
14	Kenchaiah[120]	Physician Heart	HR	CPH	+		+			+						Alcohol, FHx and medication
15	Brouwers#[121]	Prevend	HR	CPH	+	+	+	+	+	+		+			+	Cystatine, UAE, CRP, NT-proBNP, hs-TnT

¶ Variables used for mutually adjusted risk calculation; # Studies included for mutually adjusted risk calculation.

RF (Risk Factor); HR (Hazard Ratio); OR (Odds Ratio); RR (Relative Risk); FHS (Framingham Heart Study); HABC (Health Aging and Body Composite Study); NHANES (National Health Nutrition Examination Survey); ARIC (The Atherosclerosis Risk in Communities); Million P-Y (One Million Person-Year study); MESA (Multi-Ethnic Study of Atherosclerosis); CVH (Cardio Vascular Health study); EPESE (Established Population for Epidemiologic Studies of the Elderly program); CARDIA (Coronary Artery Risk Development in Young Adults); ULSAM (Uppsala Longitudinal Study of Adult men); Kuopio (Kuopio Finland study); Mt Sinai (Study at Mt Sinai); MDCS (the Malmo diet and Cancer Study in Swedish people); Physician Heart (the Physician heart study); Prevend (Prevention of Renal and Vascular End-stage Disease)

LBBB (left bundle branch block); HDL (high density lipoprotein); MI (myocardial infarction); CKD (chronic kidney disease); BNP (brain natriuretic peptide); CRP (c-reactive protein); FHx (family history); UAE (urinary albumin excretion); hs-TnT (highly sensitive troponin T.

Table appendix 2.9 -Newcastle–Ottawa scale for included studies

	Author	Study (Trial)	#1_Selection_Representativeness of exposed	#2_Sellection_of Non-exposed	#3_Selection_Ascertainment of exposure	#4_Outcome demonstration at start (★=yes)	#5_Comparability	#6_Assessment of Outcome	#7_Follow-up Long enough for outcome to occur	#8_Follow-up adequacy	Total ★
1	Ho KK[110] Kannel[80] Ho J[60]	Framingham study	★	★	★	★	★	★	★	★	8
2	Butler[79] Kalogeropoulos[104]	Health ABC study	★	★	★	★	★	★		★	7
3	He[102]	NHANES	★	★	★	★	★	★	★	★	8
4	Agarwal[78]	ARIC	★	★	★	★	★	★	★	★	8
5	Goyal[111]	Million P-Y	★	★	★	★	★	★		★	7
6	Bahrami[112] Bahrami[113]	MESA	★	★	★	★	★★	★		★	8
7	Gottdiener[103] Mujib[108]	Cardio Vascular Health		★	★	★	★★	★	★	★	8
8	Chen YT[114]	EPESE		★	★	★	★★	★		★	7
9	Bibbins-D[115]	CARDIA		★	★	★	★	★	★	★	7
10	Ingelsson[116]	ULSAM		★	★	★	★	★	★	★	7
11	Wang J[117]	Kuopio		★	★	★	★★	★	★	★	8
12	Aronow[118]	Mt Sinai		★	★	★	★	★		★	6
13	Smith JG[119]	MDCS	★	★	★	★	★★	★	★	★	9
14	Kenchaiah[120]	Physician's heart		★	★	★	★	★	★	★	8
15	Brouwers[121]	Prevend	★	★	★	★	★	★	★	★	8

Selection: No ★is given to cohort with men or women only, or with an age selection range;
Comparability: ★if risk adjusted for confounders, or with subgroup analysis of age or gender; ☆☆ if adjusted for interim myocardial infarction
Follow-up length ★only if ⩾ 5 years
FHS (Framingham Heart Study); HABC (Health Aging and Body Composite Study); NHANES (National Health Nutrition Examination Survey); ARIC (The Atherosclerosis Risk in Communities); Million P-Y (One Million Person-Year study); MESA (Multi-Ethnic Study of Atherosclerosis); CVH (Cardio Vascular Health study); EPESE (Established Population for Epidemiologic Studies of the Elderly program); CARDIA (Coronary Artery Risk Development in Young Adults); ULSAM (Uppsala Longitudinal Study of Adult men); Kuopio (Kuopio Finland study); Mt Sinai (study at Mt Sinai); MDCS (the Malmo diet and Cancer Study in Swedish people); Physician's heart (the Physician heart study); Prevend (Prevention of Renal and Vascular End-stage Disease

Table appendix 2.10 -Reasons for excluded Studies

	Reasons for excluded Studies after full text review (n=83+9=92)	
	Author, year	**Reasons for exclusion**
1	Eriksson, 1989 (Eur Heart J)	Risk estimates not meeting inclusion criteria
2	Wilhelmsen, 2001 (J Intern Med)	Risk estimates not meeting inclusion criteria
3	Ansari,2003 (Am Heart J)	risk for CV hospitolization
4	Kardys, 2006 (Am Heart J)	Risk estimates not meeting inclusion criteria
5	Gurwitz, 2013 (Am J Med)	Risk estimates for HFpEF
6	Wannamethee, 2011 (J Am Coll)	Risk estimate not meeting inclusion criteria
7	Baena-Diez, 2010 (Clinical Cardiology)	Risk estimates not meeting inclusion criteria
8	Britton, 2009 (Eur J Heart Fail)	Risk estimates not meeting inclusion criteria
9	Dunlay,2009 (Am J Med)	case matched study
10	Gupta, 2010 (Am Heart J)	No risk effect estimates
11	Kenchaiah, 2002 (N Engl J Med)	Duplication of study population (FHS)
12	Ebong, 2013 (Obesity)	Duplication of study population (MESA)
13	Vasan, 2003 (Circulation)	Duplication of study population (FHS)
14	Cesari, 2003 (Circulation)	Duplication of study population (HABC)
15	Ingelsson, 2006	Duplication of study population (ULSAM)
16	Bibbins, 2004 (Circulation)	Not an unselected population
17	Azad, 2011 (Journal of geriatric cardiology)	review article
18	Carr, 2005 (Am J Cardiol)	Not an unselected population
19	De Simone, 2013 (Nutr Metab Cardiovasc Dis)	Not an unselected population
20	Senni, 1999 (Arch Intern Med)	risk for mortality
21	Owan, 2006 (N Engl J Med	risk for mortality
22	Adlam 2005 (European Heart Journal)	Not reporting characteristics of inclusion
23	Arnlov, 2004 (European heart Journal)	Not reporting characteristics of inclusion
24	Arnold, 2005 (J Am Geriatr Soc)	Not reporting characteristics of inclusion
25	Aurigemma, 2001 (JACC)	Not reporting characteristics of inclusion
26	Babb, 2009 (AORN J)	review article
27	Barnard, 2005 (Current Cardiology reports)	review article
28	Belin, 2011 (Am J Clin Nutr)	Not reporting characteristics of inclusion
29	Bertoni, 2004 (Diabetes care)	Diabetic population
30	Bibbins, 2009 (N Engl J Med)	Not reporting characteristics of inclusion
31	Bleumink, 2004 (European Heart J)	No risk effect estimates
32	Brenyo, 2011 (Cardiol J)	Not reporting characteristics of inclusion
33	Bruch, 2006 (J Am Soc Echo)	echo and bnp for CV events
34	Bui, 2011 (Nature reviews)	review article
35	Cabrera, 2012 (Clin Interv Aging)	CV events
36	Campbell, 2003 (MJA)	review article
37	Castagno, 2012 (JACC)	Population not meeting inclusion
38	Chae,2003 (The Am J of Cardiology)	Risk estimat not meeting inclusion
39	Cowie, 1997 (European Heart Journal)	review article
40	Cowie, 1999 (European Heart Journal)	No risk effect estimates
41	Curtis, 2008 (Archives of internal Med)	No risk effect estimates
42	De Simone, 2007 (Diabetes care)	Population not meeting inclusion
43	Desimone, 2010 (Journal of Hypertension)	Population not meeting inclusion
44	Deswal, 2011 (JACC)	review article
45	Dhingra, 2010 (Arterioscler Throm Vasc Biol)	Not reporting characteristics of inclusion
46	Ekundayo, 2009 (Hypertension)	Not reporting characteristics of inclusion
47	Filippatos, 2011 (Eur J of HF)	Not reporting characteristics of inclusion
48	Folsom, 2009 (Circulation, heart failure)	Not reporting characteristics of inclusion
49	Giamouzies, 2011 (J Cardiac Fail)	review article
50	Haass, 2011 (Circulation, heart failure)	Not reporting characteristics of inclusion
51	Hagege, 2010 (Archives of Cardiovascular Dis)	Population not meeting inclusion
52	Hoffman, 1994 (Arch Intern med)	Population not meeting inclusion

53	Horne, 2010 (European Journal of heart failure)	Risk estimate not meeting inclusion criteria
54	Hsich, 2011 (JACC)	Edtorial comment
55	Jain, 2011 (Circ cardiovasc Imaging)	Risk estimate for CV disease
56	Kaczorowski, 2011 (BMJ)	Not reporting characteristics of inclusion
57	Kalogeropoulos, 2010 (Circ Heart Fail)	Not reporting characteristics of inclusion
58	Kannel, 2000 (Heart Failure Reviews)	review article
59	Kawut, 2012 (Circulation)	risk estimates for HF or death
60	Ketchum, 2011 (Congestive heart failure)	review article
61	Khatibzadeh, 2012 (International journal of cardiology)	review article
62	Krishnan, 2009 (Circ Heart Fail)	Not reporting characteristics of inclusion
63	Lam, 2011 (Circulation)	duplication of population (FHS)
64	Laugsand, 2013 (European Heart journal)	Not reporting characteristics of inclusion
65	Leung, 2009 (Journal of cardiac failure)	Diabetic population
66	Liszka, 2005 (Ann Fam Med)	Duplication of study population (NHANESI)
67	Lloyd-Jones, 2002 (Circulation)	Not reporting characteristics of inclusion
68	Loehr, 2008 (Am J Cardiol)	Duplication of study population (ARIC)
69	Luepker, 1990 (American J of Epidemiology)	Not reporting characteristics of inclusion
70	Marwick, 2006 (JACC)	review article
71	Mostofsky, 2012 (Circulation. Heart failure)	review article
72	Mujib,2012 (Ann Med)	Not reporting characteristics of inclusion
73	Okin, 2011 (Circ Cardiovasc Qual Outcomes)	Population not meeting inclusion
74	Okin, 2012 (Am J Cardiol)	Risk estimate not meeting inclusion criteria
75	Palazzuoli, 2011 (Intern Emerg Med)	review article
76	Pfister, 2012 (European Heart Journal)	Not reporting characteristics of inclusion
77	Redfield, 2012 (Heart failure clinics)	review article
78	Rod, 2011 (Am J epidemiol)	Risk estimate not meeting inclusion criteria
79	Roger, 2004 (JAMA)	Risk estimate not meeting inclusion criteria
80	Roy, 2011 (Am J Cardiol)	Propensity matched study in diabetes
81	Sanderson, 1995 (International Journal of Cardiology)	Risk estimates not meeting inclusion criteria
82	Schnabel, 2013 (European Journal of Heart Failure)	Population not meeting inclusion
83	Senni, 1998 (Circulation)	Risk estimates not meeting inclusion criteria
84	shah, 2011 (J Am Coll Cardiol)	Risk estimates not meeting inclusion criteria
85	Silver, 2003 (Congestive heart Failure)	Not reporting characteristics of inclusion
86	Sprafka, 1990 (Am J Epidemiol)	Risk estimates not meeting inclusion criteria
87	Suzuki, 2008 (Circulation. Heart Failure)	duplication of population (CVH)
88	Varadarajan, 2006 (J Am Soc Echocardiogr)	Population not meeting inclusion
89	Victor, 2004 (Am J Cardiol)	Risk estimates not meeting inclusion criteria
90	Wang, 2011 (Am J Epidemiol)	Not reporting characteristics of inclusion
91	Wang, 2012 (Circulation)	duplication of study population (FHS)
92	Yan, 2011 (JACC)	Risk estimates not meeting inclusion criteria

2.2 Cardiac Biochemical Markers

A variety of biochemical tests have been developed as cardiac biomarkers. The levels of these markers may reflect various aspects of the pathophysiology of heart failure. Cardiac biomarkers can be broadly classified into 1) neurohormonal activation, i.e. natriuretic peptides; 2) myocyte injury, i.e. cardiac troponins; 3) extracellular matrix remodelling, i.e. collagen products; 4) inflammation, i.e. cytokines and ST2 and CRP; and 5) emerging new biomarkers, i.e. adipokines and galectin3[127] and soluble micro RNA.

One of the most widely used markers are cardiac natriuretic peptides (BNP and NT-proBNP). Other emerging and promising but less common markers include soluble ST2 (interleukin 1 receptor) and intra and extra cellular non-coding microRNAs (miRNA). Although this research did not include any biomarkers for analysis, mainly due to cost issues, these three biomarkers commonly related to HF diagnosis and management are discussed in the following section. Current evidence about their association with subclinical cardiac dysfunction was also summarized accordingly.

2.2.1 Cardiac biomarker – Natriuretic Peptides

The cardiac natriuretic peptides consist of three types: atrial natriuretic peptide (ANP), brain natriuretic peptide including (BNP)/N-terminal proBNP (NT-proBNP), and C-type natriuretic peptide[128]. BNP and NT-proBNP have emerged as important markers for HF diagnosis, prognosis, and guiding treatment.

BNP is a 32 amino acid polypeptide, NT-proBNP is a 76 amino acid N-terminal fragment of BNP. These peptides are secreted into the blood stream by cardiac myocytes in response to increased ventricular wall stress, hypertrophy, and volume overload[127,129,130]. The physiologic actions of BNP are reduction in systemic vascular resistance, central venous pressure and increased natriuresis. These actions cause reduction in blood volume, systemic blood pressure and afterload in order to regulate and adjust cardiac output. BNP and NT-proBNP levels are abnormally increased in patients with HF and has been used as important markers in emergency department as well as at primary care setting. Assessment of blood natriuretic peptide levels is currently recommended by some guidelines to help in the diagnosis of HF at the time of presentation[124,131]. Over the last decade, BNP and NT-proBNP have brought significant improvement in HF disease management in both acute HF and in primary care setting [127,132-134].

2.2.1.1 BNP and NT-proBNP in symptomatic HF

In patients with symptoms, BNP and NT-proBNP had good performance for ruling out HF[135]. The level of BNP or NT-proBNP in the plasma directly relates to the severity of HF (Figure 2.7)[8]. When considering differential diagnosis, the common cut-offs used for BNP are: HF is unlikely if <100 pg/mL; HF is likely if BNP >400 pg/mL[136]. Cut-offs for NT-proBNP are: HF is unlikely if <300 ng/mL; but likely if >450 pg/mL (age< 50 years), or > 900 pg/mL (age: 50-75 years) or > 1800 pg/mL (age > 70 years)[8,137]. As the values detected can be confounded by age and gender. Age specific cutoff are listed in Table 2.11. Interpretation of test needs clinical guidance[13,130,134,138,139].[1]. In addition to being used for the diagnosis of HF, the cardiac peptides may also be beneficial in the treatment of patients with HF.

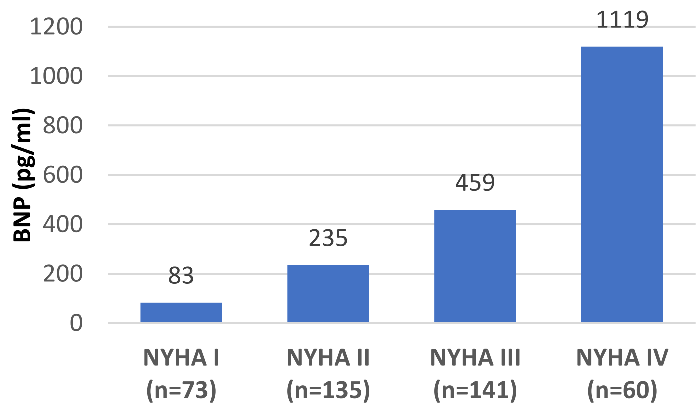


Figure 2.7 BNP level and symptom by NYHA
Adopted from Weber and Hamm, 2006;92(6):843-849

Table 2.11 Cut-off values for the diagnosis of HF

	Rule out: HF unlikely	Rule in: HF likely
BNP (ng/L)	100	400
		500
NT-proBNP* (ng/L), age<50	300	450
NT-proBNP* (ng/L), age>50	300	900
NT-proBNP** (ng/L), age<75	125	
NT-proBNP** (ng/L), age>75	450	

*(Weber and Hamm, 2006)[8], ** (Radem, 2005)[16]

Evidence on the use of BNP to monitor HF patients has been reported previously[140]. The results showed that monitoring HF using the guidance of BNP and/or NT-proBNP resulted in fewer cardiovascular deaths and total cardiovascular events than without guidance. However, a recent systematic review and meta-analysis showed the benefits of therapy guided by this test were present only in patients with HFrEF (Figure 2.8)[132].

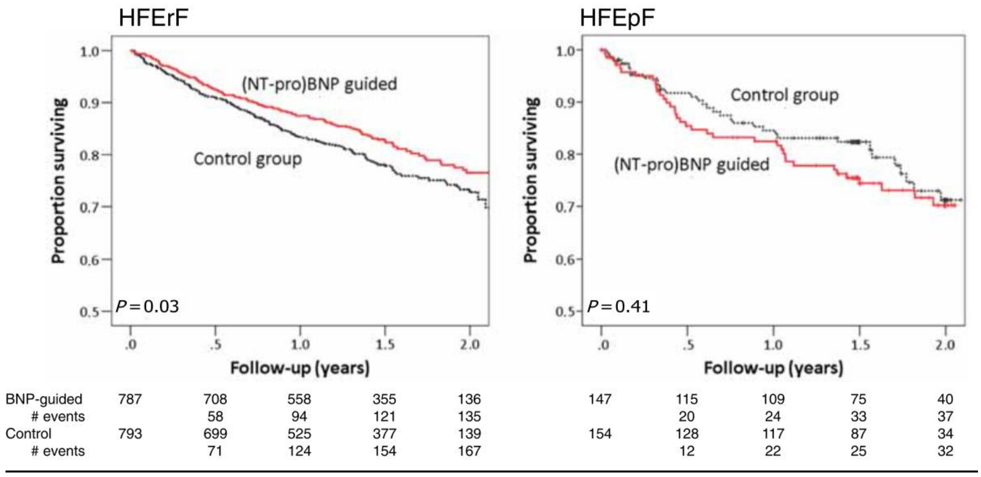


Figure 2.8 Treatment guided by (NT-pro)BNP
Adopted from Brunner-La, Eur J Heart Fail. 2015;17(12):1252-1261.

2.2.1.2 BNP and NT-proBNP in asymptomatic SBHF

In patients without symptoms, the presence of cardiac structural and functional impairment (stage B heart failure) was also associated with elevated BNP and NT-proBNP. The association with systolic dysfunction defined by reduced ejection fraction has been reported in a systematic review and meta-analysis[139]. The test sensitivity by various cut-off values is displayed in Table 2.12. The association with left ventricular hypertrophy and diastolic dysfunction was also reported [4 46,139,141-144].

Table 2.12 Test accuracy of BNP for reduced ejection fraction

		BNP/NT-proBNP	
	n	Sensitivity	Specificity
Hutcheon et al 2002 (BNP cut-off 35 pmoL/l)	304	0.94 (0.79-1.0)	0.63 (0.57-0.69)
Hutcheon et al 2002 (BNP cut-off 49 pmoL/l)	304	0.84 (0.66-0.95)	0.69 (0.63-0.74)
Kruger et al 2004 (BNP cut-off 23pmol/l)	66	0.89 (0.79-0.96)	0.56(0.42-0.68)
Landray et al 2000 BNP cut-off 5pmol/l)	126	0.88 0.73-0.96)	0.34 (0.24-0.45)

Modified from systematic review and meta-analysis by Davenport, Br J Gen Pract

However, in these asymptomatic "seemingly normal" individuals, what denotes an "elevated or abnormal" value can be ambiguous, challenging and difficult. Figure 2.9 and Figure 2.10 shows the "near normal" values which show variations in age and gender specific community individuals with systolic and diastolic dysfunction.

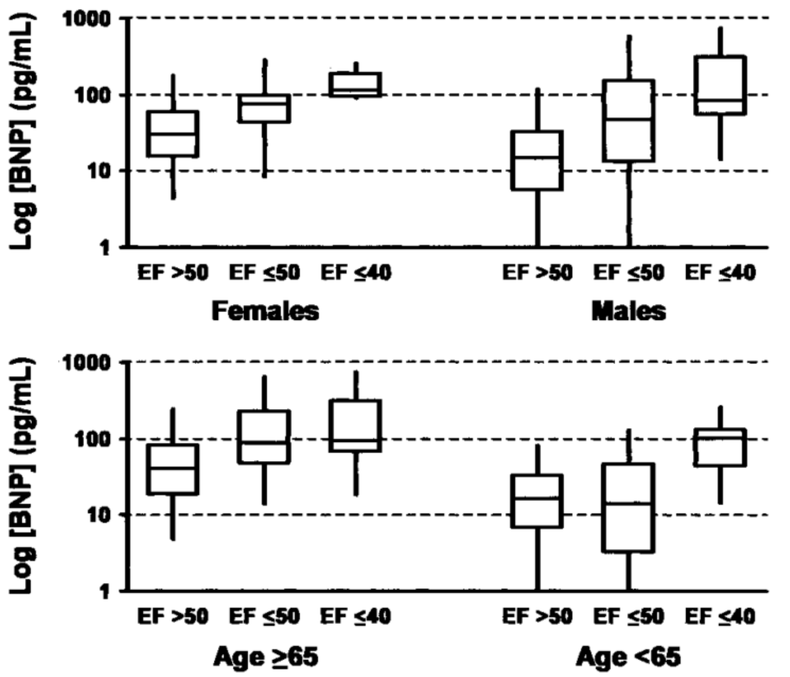


Figure 2.9 BNP and systolic function by reduced EF

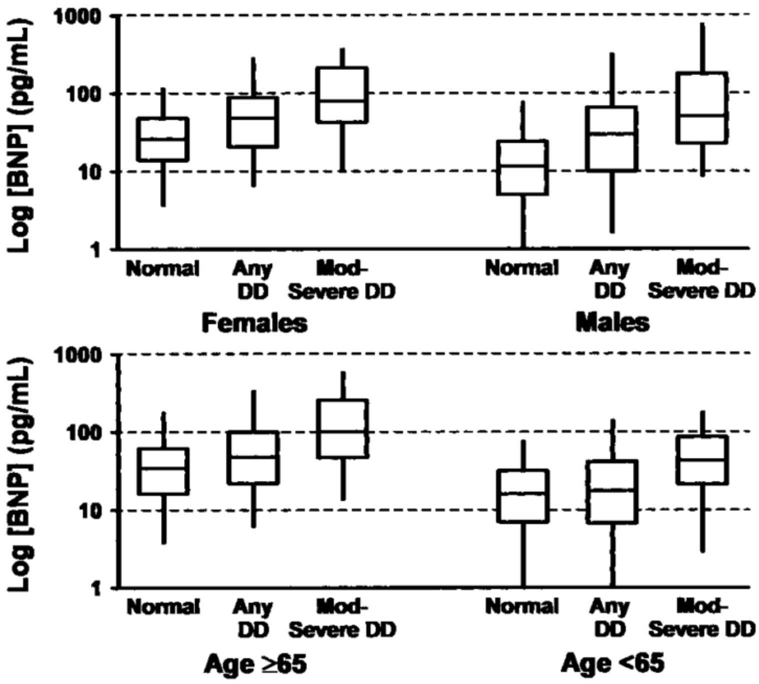


Figure 2.10 BNP levels and diastolic function

2.2.1.3 Issues about this biomarker

Regardless of whether patients have or don't have symptoms, the main concern is the issue of common confounding factors. The "normal range" can be broad and with substantial analytical and biological variabilities. This may not be important when tested values are markedly elevated in patients in advanced stages, but critical when values are at near "normal" or at upper limit of normal patient without symptoms. A few known confounding factors are summarized as follows:

First, the effect of age and gender. BNP/NT-proBNP levels are significantly higher in normal females and significantly increased with age[145,146]. Although age related comorbidities may also be confounders, the several fold differences in apparently normal individuals seemed to be physiological[145]. Age and gender stratified normal limits were suggested from the Framingham study (Figure 2.11). The limit of specified cut-offs can make clinical interpretation challenging and difficult in the context of other comorbidities.

Age (yrs)	BNP (pg/ml) Men 95th Percentile	BNP (pg/ml) Men 97.5th Percentile	BNP (pg/ml) Women 95th Percentile	BNP (pg/ml) Women 97.5th Percentile	NT-ANP (pmol/L) Men 95th Percentile	NT-ANP (pmol/L) Men 97.5th Percentile	NT-ANP (pmol/L) Women 95th Percentile	NT-ANP (pmol/L) Women 97.5th Percentile
20–49 (106 men, 152 women)	21	26	31	38	463	574	548	664
50–59 (141 men, 241 women)	21	26	31	42	550	574	615	664
60–69 (74 men, 139 women)	28	50	39	54	575	767	731	757
70+ (21 men, 37 women)	48	52	69	71	1140	1260	1000	1430
Pooling all age groups	26	34	38	54	585	698	698	783

Sample sizes are shown in parentheses. For BNP: 1 pg/ml = 0.289 pmol/L.

Figure 2.11 Proposed normal BNP levels stratified by age and gender
Thomas J. Wang et al, Am J Cardiology 2002; 90 254-258

Second, BNP/NT-proBNP levels are inversely related to BMI, in particular visceral adiposity. This is possibly related to insulin resistance and metabolic disturbance[142,147,148]. Visceral adiposity is highly prevalent in non-ischemic stage B heart failure, so the variability of this test is therefore particularly challenging.

Third, compared with subjects with cardio vascular risk factors, the value of this marker was found to be limited in seemly healthy individuals[134]. This indicates a limited value of this test in early disease stage for screening in the general population.

Fourth, BNP was found not to be an optimal test for mild systolic dysfunction, nor for diastolic dysfunction - even with age and sex-specific discriminatory values[13]. BNP was increased to a lesser extent in subjects with diastolic dysfunction than LV hypertrophy or LV systolic dysfunction. Individuals with sole diastolic abnormality displayed BNP concentrations at the control level[130], indicating BNP can be near normal in those with evidence of early cardiac dysfunction. Thus, the value of BNP is undetermined in early disease stage (SBHF).

Fifth, head-to-head comparison of BNP and NT-proBNP results suggested BNP to be a better indicator than NT-proBNP in population screening for cardiac dysfunction or diagnosis of clinical heart failure[142]. The cause of the difference and the associated clinical impact has not been determined. It is unknown whether analytical or biological variability is the underlying cause. However, this is an important issue in the context of community screening.

2.2.1.4 Community screening using BNP – current evidence

In the hope that this simple and relatively inexpensive but feasible test may be ideal to detect cardiac dysfunction in the community, screening using BNP/NT-proBNP for reduced EF has been reported in multiple large population studies. These are the Framingham study [2], Olmsted County population[13,134], the MONICA cohort[1], the Multi-Ethnic Study of Atherosclerosis (MESA) cohort[144] and the Atherosclerosis Risk in Communities (ARIC) study cohort[149]. The overall test performance for diagnosis of left ventricular dysfunction was sub-optimal. In a meta-analysis, Ewald[142] systematically assessed the diagnostic performance and characteristics of BNP or NT-proBNP in thirteen community based studies (Table 2.13).

Table 2.13 Community screening studies using BNP and/or NT-proBNP

	Author	Reference standard	Assay	Age (SD)	% (f)	Sen.	Spe.	DOR
1	Luchner[1]	LVFS<28%	BNP	58	56	55	86	7
2	Vassan[2] male	LVEF <40%	BNP	58	0	65	86	11
	female				100	80	90	36
3	McDonagh[4]	LVSD undefined	BNP	51(14)	51	77	87	21
4	Hobbs[6]	HF	BNP	66 (11)	48	80	88	30
5	Smith[9]	LVSD undefined	BNP	76 (4)	n/a	92	65	21
6	Ng[10]	Wall motion score>2	BNP	63	44	88	90	68
7	Groenning[11]	LVEF<40%	NT-proBNP	68	57	76	67	7
8	Aquilar[12]	LVEF<50%	NT-proBNP	66	54	92	68	22
9	Redfield[13]	LVEF<40%	BNP	62(11)	52	90	77	29
		LVDD				44	91	8
10	Hedberg[14,15]	LVEF<40%	BNP	75	50			29
11	Hutcheon[17]	LVSD undefined	BNP	79	65	97	38	8
12	Epshteyn[18]	LVSD+DD	BNP	54(16)	4	75	76	17
13	Bibbins-D[19]	EF<45%	BNP	69(10)	8	60	47	7
		EF<55% or DD	BNP	69(10)	8	44	53	5

Modified from Ewald. Internal Medicine Journal 38 (2008)101-113.
LVFS: left ventricular fractional shortening; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic dysfunction; HF: hear failure; DD: left ventricular diastolic dysfunction; DOR: diagnostic odds ratio.

The potential causes of suboptimal performance of natriuretic peptides in community screening of stage B heart failure are multiple. As discussed in the previous section, in the presence of multiple common confounding factors, the cut-point used was a major limit. Besides, reduced LVEF was used as marker of cardiac dysfunction and the prevalence of this marker in the community is low. Given the poor test performance, there seems to be a concern regarding the value of the test for initial screening for subsequent echocardiogram, as it may overwhelm the echo service[1,2,13,142].

The issue of preserved versus reduced ejection fraction in both asymptomatic and overt HF further complicates the test performance. In particular, the value of natriuretic peptides in guiding therapy in diagnosed HF patients has shown benefit in patients with HFrEF but not HFpEF[132]. However, this is beyond the scope of this research and will not be discussed further. A summary of pros and cons of BNP/NT-proBNP test is listed in Table 2.14.

Therefore, considering the current evidences as mentioned above and the potential high costs of these tests in our study, we chose not to include these markers in this thesis.

Table 2.14. Pros and cons of BNP/NT-proBNP test

	Pros	Corns
Diagnosis	Good to rule out HF, especially in acute HF. Simple test in ED	Not good to rule in HF. Low level cannot exclude HF
Cut point and confounding factors	Manufacturer recommended 100pg/mL as cut-off to rule out.	• No single cut-point, most authors self-defined cut points based on study sample • Should consider confounders: age, gender, obesity, ethnicity, renal function and AF • Large biological variability, serial tests need to consider confounding factors
Predicting outcomes:	• Despite the differences in baseline models and cut-points, lengths of FU, both test show predictive value for all outcomes • High levels relate to severity and worse outcome	Serum levels do not change rapidly with changes in disease status

2.2.2 Cardiac biomarker – Soluble ST2

In addition to natriuretic peptides, new emerging cardiac biomarkers are gaining attention for their value in the diagnosis and prognosis of heart failure. Among these, ST2 is a soluble protein, a family member of interleukin-1 receptor, expressed by the heart in response to myocardial damage. There are two ST2 isoforms: transmembrane bound ST2 and soluble, i.e. circulating ST2. Interleukin-33 is the ligand for both isoforms, and binding to the transmembrane form of the receptor exerts a protective anti-hypertrophic, anti-fibrotic effect on cardiomyocytes[150,151]. Soluble ST2 (sST2) binds and removes interleukin-33 from the circulation, thus decreasing activation of the transmembrane receptor and potentially promoting adverse myocardial remodelling and fibrosis[150,151]. According to the approval of the US Food and Drug Administration (FDA), the normal cut-off value is >35 ng/mL.

2.2.2.1 Soluble ST2 in symptomatic patients with HF

In patients with acute or chronic heart failure, the American College of Cardiology/ American Heart Association guidelines recommend measurement of sST2 for additive risk stratification[152,153]. High sST2 levels are associated with an increased risk for HF progression, rehospitalisation, heart transplantation and death. These risks are independent of traditional and biochemical risk factors including BNP and NT-proBNP[154]. The advantage of using sST2 over BNP and NT-proBNP includes the following: 1) sST2 is not adversely affected by common confounding factors like age, gender, body mass index, atrial fibrillation and has a single cut point. 2) sST2 shows good prognostic value regardless of LVEF[155]. 3) In HF patients with low NT-proBNP levels, elevated sST2 was able to stratify the highest risk patients and provided prognostic value[156]. However, in the presence of low sST2, natriuretic peptides did not predict mortality[156]. Comparison of cumulative hazard of death in patients with acute HF stratified by sST2 levels and NT-proBNP is summarized in Table 2.15. 4) Serial measurement assessing disease progression over time, sST2 provided with a better "reference change value" over BNP and NT-proBNP, which is likely to detect true disease change rather than biological variability[157-159].

Table 2.15 Mortality rate in acute HF stratified by ST2 and NT-proBNP

NT-proBNP	Soluble ST2	
	Below Median	Above Median
Below median	10%	40%
Above median	28%	56%

Cumulative rate at 1 year follow up. Modified from Rehman SU et al, J Am Coll Cardiol 2008;52(18):1458-1465.

2.2.2.2 Soluble ST2 in community asymptomatic patients with SBHF

Evidence of sST2 in predicting incident HF in the community was evaluated in several large population studies including Framingham[160], Cardiovascular Health[161] and FINRISK97[162]. Findings from these studies showed that, although associated with older age, male gender and myocardial injury and other fibrosis markers, the predictive value for new HF in the presence of other risk factors and biomarkers was only modest[161,162]. Therefore, sST2 may not be a useful predictor for incident HF and cardiovascular outcome in the community[160].

2.2.3 Cardiac biomarker – MicroRNA

The term "microRNA" (miRNA) was first described in 1993[163]. After this discovery, scientists began to recognize its importance as a regulator in gene expression. MiRNAs are small non-coding strands of (approximately 17-25) nucleotides. The main role of miRNAs is to regulate gene expression by either initiating translational repression or degradation of messenger RNAs (mRNAs)[164]. The effects of miRNAs on repressing mRNA translation take place inside cells. However, in 2008, miRNAs were discovered outside cells and in circulating blood[165]. These extracellular circulating miRNAs are remarkably stable and may be used as circulating biomarkers for diseases. Based on current knowledge, there are at least 2588 mature human miRNAs identified and listed in "miRNBase" (mirbase.org). Currently, circulating miRNAs are emerging as important biomarker for cardiovascular diseases including heart failure for their diagnosis, prognosis and more importantly as therapeutic targets (Figure 2.12).

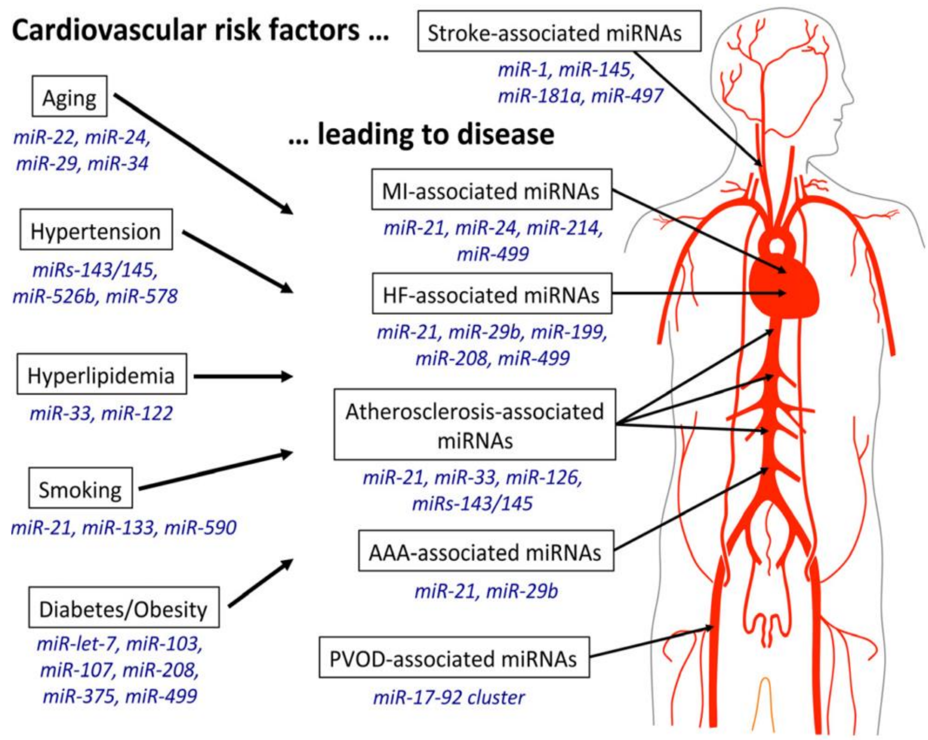


Figure 2.12 Micro RNA and Cardiac vascular risk factors and disease
Adopted from Maegdefessel et al, J Intern Med. 2014;27(6):633-644.

In the field of miRNA biomarker assessment, the sets of miRNAs used for evaluation are defined as signatures. Combining two or more miRNA biomarkers as a defined set can enhance discriminatory power. For instance, in a two-step screening study, Vogel et al found a signature of eight miRNAs (miR-520d-5p, miR-558, miR-122, miR-200b, miR-622, miR-519e, miR-1231 and miR-1228) can reliably predict the diagnosis of HFrEF with an AUC of 0.81[166]. He also found the most power single miRNA signature for HFrEF was miR-558, followed by miR-122 and miR-520d-5p[166].

2.2.3.1 Micro RNA in HFrEF and HFpEF

Pathophysiologically, HFpEF is the clinical manifestation of LV diastolic dysfunction. In order to assess whether circulating miRNAs can be utilized as biomarkers in the detection of HFpEF, in a differentiated diagnosis compared to HFrEF, Nair has recently found miR-454, miR-500 (both down-regulated) and miR-1246 (up-regulated) were significantly dysregulated in HFpEF. Their findings indicated that circulating miRNAs can serve as biomarkers to identify and possibly to guide therapy for this clinically most challenging disease phenotype[167]. Similarly, Wong et al had identified 344 miRNAs dysregulated between HFpEF, HFrEF and healthy controls[168]. These findings has been reported in another recent study by Watson et al in a similar study cohort and further validated in a larger data set[169]. These analyses showed various miRNA signatures are useful for HF and also in the differentiation of HFpEF from HFrEF[170].

2.2.3.2 Micro RNA in cardiac hypertrophy and fibrosis

Cardiac remodelling and fibrosis are important factors in the development of ventricular wall stiffness with compromised ventricular contractility and compliance. The expression of miRNAs is directly linked to the progression of HF. Although important, current evidence is largely based on experimental models. Several studies reported altered miRNA levels in cardiac hypertrophy and induction of cardiac hypertrophy by alterations of specific miRNAs[171]. Especially miR-1[172], miR-21[173], miR-133[173], miR-195[174], miR-208[175] were proven to be involved in regulation of cardiac hypertrophy.

Cardiac fibrosis is a common phenotype and found in several cardiac diseases including myocardial infarction and heart failure. Cardiac fibrosis is characterized by the adverse accumulation of collagens and other extracellular matrix proteins. In a transgenic mouse model, miR-21 was discovered as a key regulator of signalling pathways in cardiac fibroblasts controlling the extent of cardiac hypertrophy and interstitial fibrosis[176]. Several other miRNAs have been identified as also targeting collagens and relating to cardiac fibrosis including miR-24[177] and miR-29[178].

2.2.3.3 Long non-coding RNA in cardiovascular disease

Long non-coding RNA (LncRNA) are currently defined as transcripts greater than 200 nucleotides without known protein-coding function[179]. Recent reports have started to reveal the importance of LncRNA in cardiac development and their involvement in HF. However, the clinical application of this marker is still at an early stage and little is known about the specific function of these transcripts Table 2.16.

Table 2.16 IncRNAs in cardiovascular disease

Disease	IncRNA	Patient number	Validation	reference
Myocardial infarction	HIF1A-AS2, ANRIL, KCNQ1OT1, MIAT (STEMI), MALAT1	274 STEMI/140NSTEMI/86control	Correlation to Troponin	Vausort[3]
Heart failure	LIPCAR	Screening in 15/15 LVM, validation in 87 ICM, w/139 ICM w/o LVM	Associated with future CV death	Kumarswamy[5]
Coronary artery disease	CoroMarker	221 CAD/187 control	Expression analysis vs, a variety of other CV disease	Yang[7]

2.2.3.4 Micro RNA in community cohorts

There is currently little evidence available in community screening using miRNA as a screening tool. The only study of miRNA in a community cohort was performed in the Framingham Heart study (FHS) cohort of 2391 participants with measuring 159 miRNAs. The study was aimed to understand the comparability of cellular and extracellular sources of miRNA expression[180]. Findings from the study showed that plasma and blood miRNA levels are divergent and may reflect different biological processes and disease associations.

2.2.3.5. Micro RNA and targeted therapeutics

The discovery of circulating miRNAs has provided new windows for novel drug development by the administration of extracellular miRNAs. This includes reparative miRNA therapies and/or preventative therapies. Low expression levels of miRNAs can be restored with miRNA mimics, exogenously using adeno-associated viruses, subcutaneously and directly into the circulation[181]. The outlook for the clinical application in heart failure remains promising, with ongoing phase II clinical trials of inhibitory molecules has been carried out in non-cardiovascular fields.

In conclusion, miRNAs are increasingly recognized to play important roles in cardiovascular disease, including heart failure. MiRNAs are detected in the circulation, and are proposed as potential diagnostic and prognostic biomarkers in HF. However, their role and function in the circulation remains to be resolved.

2.3 Electrocardiogram

Electrocardiography (ECG), similarly to biomarkers, is potentially a suitable screening tool at primary care level to pre-select individuals for further echocardiography. Although the overall diagnostic sensitivity is known to be low for prediction of echocardiographic markers[182,183], ECG has its unique feature as a feasible and less costly diagnostic tool in the community, comparable to bio-markers[139].

The role of ECG markers in the process of community screening will be analysed and discussed in **Chapter 7** (Association between ECG and echo markers and outcome) of this thesis.

2.4 Hand-Held Echocardiography

Given the cost and availability of the standard echocardiography, a hand-held ultrasound (HHU) system may able to provide a potential substitute. A modern HHU device is characteristically lightweight, portable and may fit into a coat pocket. Most HHU devices provide B mode grey-scale imaging, some with colour Doppler, but not spectral Doppler. HHU can play an important role in structural cardiac evaluation.

Although there has been growing interest in the role of HHU as a screening tool in the community, the main limitations relate to its imaging capabilities relating to evaluation of non-ischemic stage B heart failure. Other than assessing LV ejection fraction, the current HHU system does not provide assessment of diastolic functional assessment and speckle tracking analysis for early systolic alteration[184,185]. As these advanced imaging modalities, mainly spectral Doppler, tissue Doppler and speckle tracking echocardiography, are key elements in the assessment of early cardiac dysfunction, this represents an important limitation in the community detection of non-ischemic stage B heart failure. Therefore, we did not include the application of HHU in this Thesis.

Postscript

Findings from this chapter suggest that a variety of risk factors are known to be associated with HF, the strongest association of non-ischaemic factors are diabetes followed by age, hypertension, smoking, male gender and increased BMI. Current cardiac peptide and other biomarkers may not be suitable in community screening with largely near normal cardiac function.

The next chapter will describe the TasELF study (Tasmanian study of echocardiographic detection of stage B heart failure – a population based sample used for this thesis. The chapter will also describe the methodology of echocardiography, electrocardiography, questionnaires and functional capacity assessment using 6-minute walk test.

Chapter 3

Methods

Chapter 3. Methods

Introduction

This thesis aimed to show the benefit of imaging testing by screening at-risk subjects from the local community. The screening clinic included comprehensive clinical evaluation, standard questionnaires, assessment of functional capacity using 6-minute walk test (6MW), a 12 lead electrocardiogram (ECG) and comprehensive echocardiography.

This chapter describes these relevant methodologies accordingly:

1) Overall study design of Tasmanian Study of Echocardiographic Detection of Left Ventricular Dysfunction (TasELF) - a randomized controlled trial with CONSORT (Consolidated Standards of Reporting Trials) check list.
2) Standard echocardiography and relevant imaging modalities.
3) Standard questionnaires used in this research for the assessment of activity status, symptoms and quality of life.
4) Standard method used for 6-minute walk test.

More specific methods used for each topic can be found in the respective studies presented in the subsequent chapters.

3.1 TasELF trial

The Tasmania Study of Echocardiographic Detection of Left Ventricular Dysfunction (TasELF)

No evidence is available about the benefit of early identification and early intervention in those at high risk of heart failure patients to delay or to prevent progression to clinical overt heart failure.

3.1.1 Overall Study Design

The study was designed as a Randomized Controlled Trial (RCT) of imaging modalities. Stage A heart failure patients were recruited from the local community. They were randomized into two screening imaging arms. The advanced Imaging arm measured global longitudinal strain (GLS) and diastolic function assessment. The presence of either one or in combination was used to define the presence of stage B heart failure. Conventional imaging involved measurement of left ventricular ejection fraction alone, and reduced ejection fraction was defined as the presence of stage B heart failure.

Treatment were advised in the presence of stage B heart failure. The prognostic implications were explained in face to face discussion between patient and cardiologist. Treatment titration plan and guidance for monitoring were also shared with the patient’s general physician.

Participants were followed regularly according to study protocol for process evaluation and for outcome.

The overall study flow and design are summarized in Figure 3.13

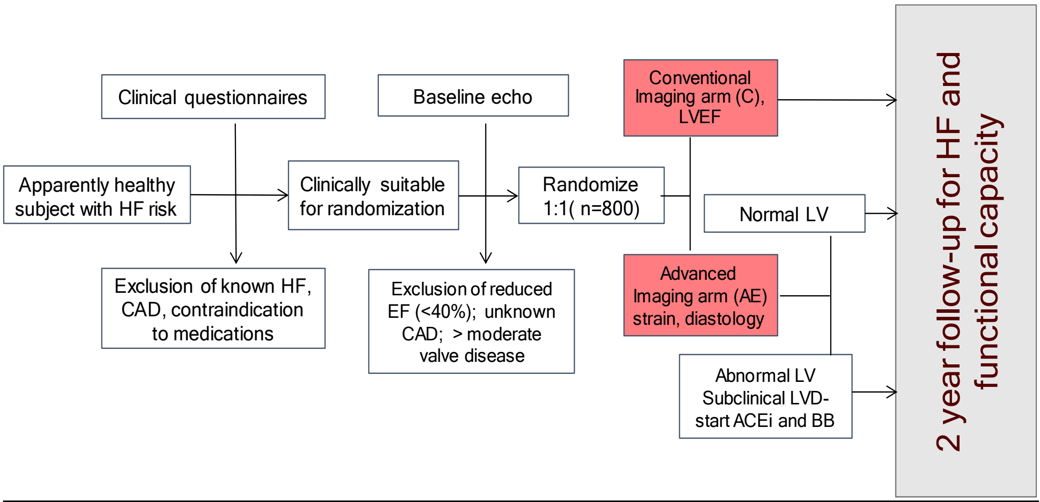


Figure 3.13. Study design and patient flow
Patient selection and randomization to Advanced imaging arm (AE) and Conventional imaging arm (C) with subsequent usual care or intervention in stage B patients.

3.1.2 Sample Calculation

The total sample was calculated to be 800 with 400 in each arm. Sample power calculations were based on the following: 1) previously reported 25% cumulative rate of incident heart failure (new heart failure) among patients with evidence of stage B heart failure under usual care[57]; 2) expected minimum follow-up time of 2-years from the last recruitment; 3) a 50% reduction of incident heart failure among the treated group (n=186) compared with usual care (n=186), to provide two-sided $\alpha=0.05$ and 80% power to document benefit of therapy; 4) expected 7.5% annual rate of loss of contact; 5) expected abnormal cardiac function present in ~50% of those under advanced imaging modality for screening (Table 3.17).

Table 3.17 Power calculation of study samples.

	Heart Failure therapy	Usual care
According to power calculation	186	186
Drop-outs (7.5% per year x 2 years)	28	28
Normal Cardiac function 50%	186	186
	400	400

3.1.3 Target Population

We studied community individuals at risk of heart failure. Three heart failure risk scores are available, the Framingham heart failure risk score[80]; the Health ABC heart failure risk score[79] and the ARIC heart failure risk score[78]. However, each has limitations, either due to the population the score was derived or the need of biomarkers for calculation. Therefore, the selection of the target population was not based on these scores.

Data from our systematic review and meta-analysis allowed us to quantify and compare each stage A heart failure risk levels, but was not able to calculate the absolute risk of each individual. We selected patients $\geq$ 65 years with risk factors for heart failure.

Target population and selection was performed according to American College of Cardiology/American Heart Association Guideline for the Diagnosis and Management of Heart Failure in Adults)[25] (Figure 3.14). We selected the non-ischemic stage A heart failure risk factors: hypertension, diabetes, obesity, metabolic syndrome, using cardiotoxins and family history of cardiomyopathy.

3.1.4 Length of Study

We planned 24-month of recruitment and 24-month of follow-up from the last recruitment. The median follow-up time was planned to be 36 months.

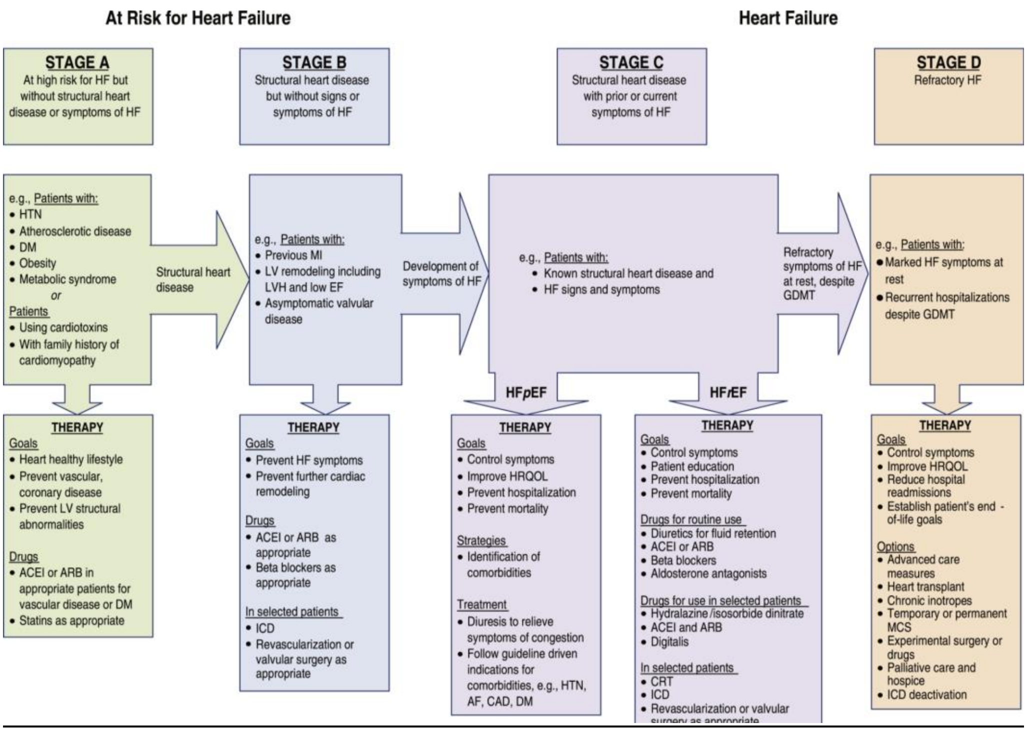


Figure 3.14 Stage in the development of heart failure.
Adopted from Hunt et al. JACC Vol. 53, No. 15, 2009

3.1.5 Means of recruitment

Recruitment was conducted through announcements in local public places (community centres); advertisement in local media (radio/TV); organized community outreach by visiting the local Lions/Rotary events. These activities had influences not only on our potential participants, but also on their neighbours, friends and family who either volunteered or helped to identify at risk subjects.

3.1.6 Inclusion Criteria

• Age: at least 65 years of age (≥ 65 years)

• The presence of at least one of the following 1) Hypertension, based on SBP>140 mmHg and self-report of HTN including anti-hypertensive medication; 2) type 2 diabetes mellitus, based on self-report of diagnosis including medication; 3) obesity, based on body mass index (BMI) ≥ 30 g/m2; 4) previous potentially cardio-toxic chemotherapy; 5) familial cardiomyopathy; 6) previous history of heart disease (but not existing heart failure).

3.1.7 Exclusion Criteria

• Unable to provide written informed consent to participate in this study

• History of previous heart failure, baseline NYHA >2

• History of coronary artery disease (previous myocardial infarction, myocardial revascularization, coronary stents, positive stress test, or echocardiographic screening of LVEF<40%.

• Known history of more than moderate valvular heart disease

• Systolic BP <110mmHg, pulse <60/minute

• Serious life-threatening disease (anticipated life expectancy <2 years)

• Pre-existing treatment with both investigational drugs (ACEi/ARB and Beta blocker) classes, or one class at maximum dose

• Contraindications/Intolerance of either beta blockers or ACEi/ARB,

• Participating in any other clinical research trial

• Atrial fibrillation (Unable to determine diastolic function)

• Inability to acquire interpretable images (identified from baseline echo)

3.1.8 Recruitment

Means of recruitment were as follows:

- Announcement in public places including Lions/Rotary/Men's shed
- Recommendation by GP and leaving trial flyers in GP's office
- Advertisement and public talk in local media (radio/TV)
- Facebook web page

Recruitment was carried out during September, 2013 – November, 2015. Echo screening outreach service were held in 9 community locations: Huonville, Oatlands, Burnie, Deloraine, Devonport, Geeveston, Latrobe, Launceston, Longford, Menzies (Figure 3.15).

Figure 3.15 TasELF outreach echo clinic locations
★ TasELF clinics held: Huonville, Oatlands, Burnie, Deloraine, Devonport, Geeveston, Latrobe, Launceston, Longford, Menzies

The total number of clinic days were 160 and the number echocardiograms performed (including baseline screening and partial follow-up scan at 1 year) was 953 (Table 3.18). The participants were across most areas of the State of Tasmania, covering >97 postal areas. Many of them had to take a long drive to travel from their home to these clinic sites. For instance, participants travelled from Queenstown to Burnie, from King Island to Launceston, from St Helens to Launceston, from Swansea to Hobart, from Smithton, George Town and Scottsdale to Burnie, Latrobe and Launceston to attend clinics.

Table 3.18 Summary of TasELF clinic days and number of participants

Location	Clinic (days)	Participants (number)
Burnie	8	69
Deloraine	2	20
Devonport (Latrobe)	11	59
Geeveston	2	18
Huonville	2	18
Launceston	20	167
Longford	2	17
Oatlands	2	26
Menzies	100	559
Total	149	953

3.1.9 Clinical Evaluation

A total of 1026 potential participants applied to participate. All completed clinical screening. All subjects underwent a clinical evaluation for eligibility (Figure 3.16**)** and risk assessment. This included clinical history, medication status and standard questionnaire to assess baseline general health status (EQ5D), activity (Duke Activity Score Index) and heart failure symptoms (MLHFQ). We excluded 378 participants not meeting clinical inclusion criteria, who did not proceed to echocardiography. The detailed causes of exclusion are summarized in Figure 3.16.

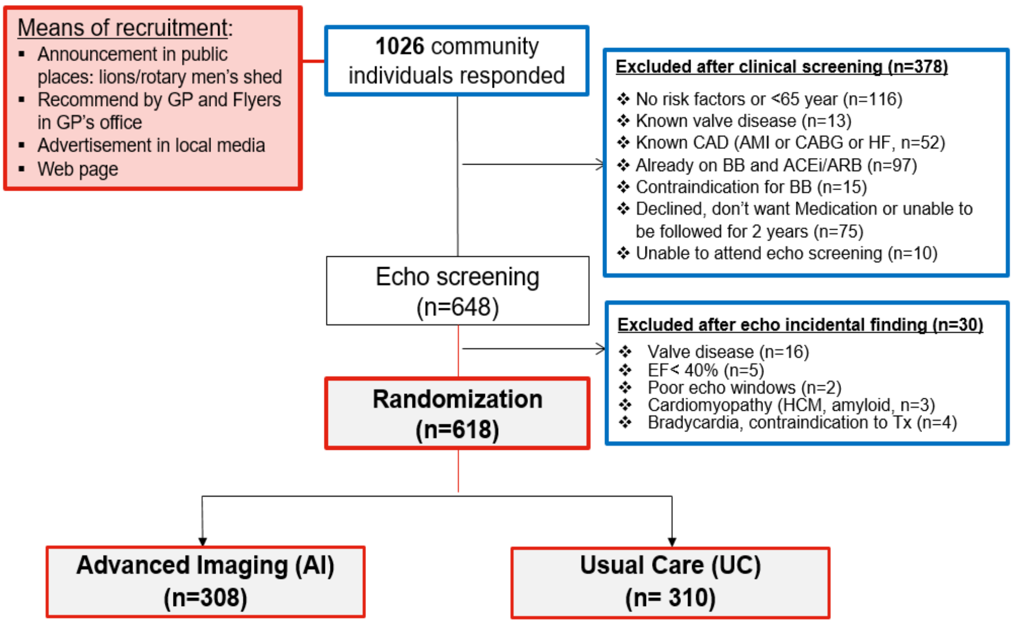


Figure 3.16 Summary of TasELF recruitment and inclusion

3.1.10 Echocardiographic evaluation and inclusion

Of the 648 (64%) who met clinical inclusion criteria and were eligible for baseline echo screening, 30 were found to have previously unknown cardiac conditions (listed in Figure 3.16) and were excluded after echocardiography. Left ventricular abnormal systolic function (EF <40%) or more than moderate valvular disease were excluded. Details of the echocardiographic assessment protocol are discussed in **section 3.2.** This process left 618 eligible for randomization.

3.1.11 Randomization

The randomization followed a Prospective Randomized Open Blinded Endpoint (PROBE) design[186]. This approach was adopted in consideration of the safety of intervention titration in these elderly participants. The monitoring of potential tolerance and side effects were allocated to the patients' primary care giver. The outcomes including new heart failure events, exercise capacity, symptom status, general health and heart failure specific quality of life were to be assessed by investigators blinded to allocation status.

Randomization was done using a central web based system at Menzies Data Management Centre (using a computerized protocol). The randomization used adaptive allocation and was stratified according to baseline diabetes status. The people receiving the treatment, the people assessing the outcomes and the persons analysing the data and results were masking/blinding at randomization.

The 618 eligible participants were randomized to two imaging strategies: Imaging guided care using advanced imaging markers (AE) versus usual care (UC) arms. Advanced imaging was characterised by the inclusion of global longitudinal strain (GLS) and diastology evaluation. The presence of a global longitudinal strain < 18%[85] or diastolic dysfunction were used to advise AE participants of LV dysfunction in a face to face discussion with a cardiologist and communicated to their GP for initiation of treatment and for treatment monitoring as discussed in the following section.

UC arm was limited to evaluation of left ventricular ejection fraction. All participants in this arm had ejection fraction >40%, advice to initiate treatment in this arm was based on individual history. Treatment implications of abnormal echo findings were explained in a face to face discussion with a cardiologist and communicated with their primary physician.

3.1.12 Treatment strategy and titration

Subjects with an abnormal echocardiographic findings were identified as having stage B heart failure and only stage B heart failure participants were advised to initiate treatment under the supervision of their physician. The physicians were given a detailed study protocol, prognostic implications of individual findings according to current guidelines, treatment titration plan and guidance for monitoring adverse events and severe adverse events according to the study protocol.

In the presence of stage B heart failure, by protocol, these patients were initially treated with Ramipril at dose of 1.25 or 2.5 mg (according to baseline systemic arterial pressure), once or twice a day, and gradually up-titrated to 10 mg/day, or to the maximal-tolerated dose (Table 3.19). In patients receiving at least 5 mg/day of ramipril, metoprolol was started at an initial dose of 12.5 mg/day and progressively up-titrated to the maximal dose of 100 mg/day. Additional heart failure therapy (diuretics, anticoagulants or antiarrhythmic drugs) were given at the discretion of the physician. Treatment records regarding drug accountability were checked by self-report questionnaires.

Table 3.19 Medication titration Schedule

Weeks since starting therapy	0	2	4	6	8	10	12	14	16
Ramipril (mg/d)*	1.25	2.5	5	5	5	5	5	5	10
Metoprolol (mg/d) **			12.5	25	37.5	50	75	100	

*if patient is already on an ACEi or ARB, there no need to change, however, please up-titrate to the maximal tolerable dose.
** if patient is already on another B-Blocker, there is no need to change, please up-titrate to the maximal tolerable dose.
During treatment, patients need to be seen every 2 weeks during the up titration phase. At each of these visits, symptoms status (fatigue, dizziness), blood pressure and heart rate need to be obtained. If patients complain of side-effects or the heart rate is <50 beats per minute, the dose should be reduced to the prior to the last increment.
Discontinuation criteria: symptoms consistent with cardiac dysfunction (dyspnea, reduced exercise capacity), side effects of therapy (fatigue), progression of cardiac dysfunction (EF<50%, dyspnea, reduced exercise capacity)

3.1.13 Usual Care

Participants with normal left ventricular ejection fraction and free of significant valvular abnormalities from conventional imaging arm, or participants with normal diastolic function and normal global longitudinal strain were advised to follow their current standard care under their general physician. In the case of progression to heart failure, referral to cardiologist and on treatment were provided by their general physician.

3.1.14 Safety Evaluations

Safety evaluations were performed by recording adverse events and serious adverse events, and monitoring vital signs and physical examinations. The following cardiac and non-cardiac events were considered as adverse or serious adverse events:

• Sudden death

• Death resulting from a cardiac cause

• acute pulmonary oedema

•Overt heart failure requiring hospitalization

• Life-threatening arrhythmias requiring treatment

• Conduction disturbance requiring a permanent pacemaker

3.1.15 Follow up

All subjects were tracked by phone calls on the 3rd, 6th- 12th month for possible symptoms and intervention related adverse effect.

At 12 month follow up, potential HF symptoms were assessed through regular follow-up phone calls, followed by symptom surveillance questionnaires and clinical visits. During the process, information on all-cause hospitalization was monitored and collected. Possible heart failure signs and symptoms were reviewed by 3 independent cardiologists, and heart failure diagnosis was confirmed using the Framingham criteria for HF[110].

3.1.16 Endpoints

At one year, the primary composite end points were new onset of heart failure and death of cardiovascular causes.

The diagnosis of new heart failure used Framingham criteria. The Framingham diagnostic for clinical congestive heart failure was described in chapter 1 and section 1.2.2 (Table 1.1)**.**

3.2 Standard Echocardiographic Evaluation

3.2 Standard Echocardiography

3.2.1 Standard echo protocol for screening

Standard transthoracic 2D and Doppler echocardiographic studies were performed using standard equipment (Siemens ACUSON SC2000, Siemens Healthcare, Mountain View, CA) and transducer (4V1c, 1.25-4.5 MHz; 4Z1c, 1.5-3.5 MHz) in accordance with the American Society of Echocardiography (ASE) guidelines [187,188]. Images were digitally recorded. The standard TasELF echo screening and evaluation protocol is summarized in (Table 3.20).

Table 3.20 Standard TasELF echocardiography screening protocol

Standard screening protocol, acquire with extended RR interval, Store with and without measurements; on-line measurements

	Views	2D	Colour	M-mode	PW	CW	TDI	strain focus	3D focus	Provide Measurements
1	Plax	1	1	1						LVOT diameter, LVMi, 2D LV linear, AO root size
2	RV inflow	1	1			1				TR Vmax
3	RV outflow	1	1			1				PV, PPG
4	PSAX-AV	1	1	1						
5	PSAX-RVOT	1	1		1	1				RVOT, PV
6	PSAX-TV	1	1			1				TR Vmax
7	PSAX-MV							1		
8	PSAX-pap							1		
9	PSAX-apex							1		
10	AP4	1	1	1	1	1	1	1+1	1	MV/MR, Simpson LV/LA, TDI (annular: Lateral, Septal, RV), TAPSE, TR, LV tracking for strain
11	AP5	1	1		1	1				AV/AR, LVOT
12	AP2	1	1					1+1		Simpson LV/LA, LV tracking for strain
13	AP3	1	1					1+1		LV tracking for strain
14	Sub-costal	1	1		1					HV Doppler
15	Sup-sternal	1	1							

(1+1): LV zoom and LA zoom

3.2.2 M-mode assessment

Standard M-mode assessment was performed in the parasternal long axis, or long axis guided parasternal short axis views. The measurements of left ventricle were septal wall, internal dimension and posterior wall during end diastole were followed the American Society of Echocardiography's recommendation for cardiac chamber quantification[187] and for the calculation of left ventricular mass (Figure 3.17). In the cases when a perpendicular was impossible, 2-D linear measurement was used for this calculation. Echo-LVH was defined as LVMi>115 g/m^2 in men and >95 g/m^2 in women[187].

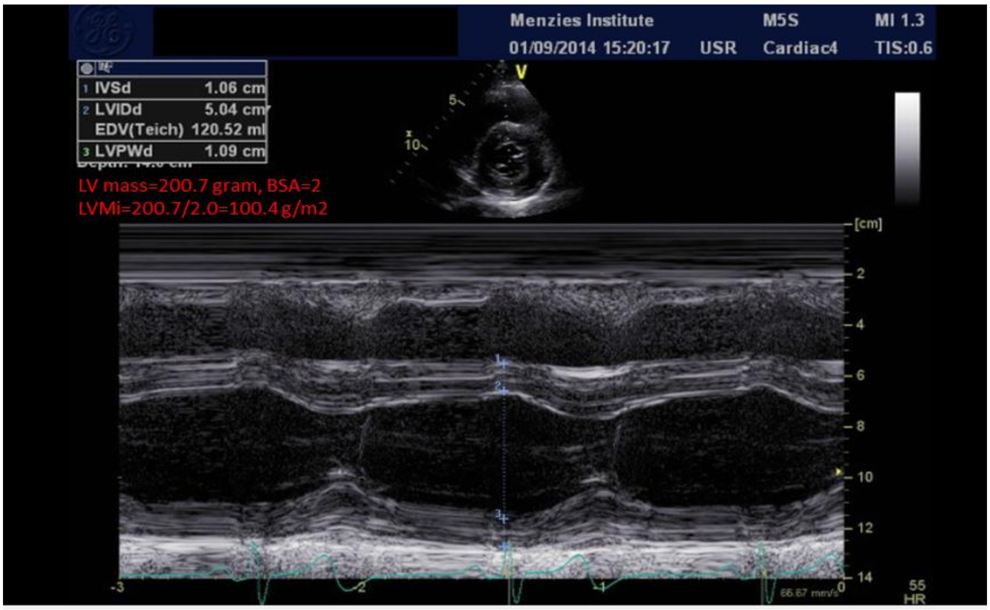


Figure 3.17 M-mode measurement of left ventricular mass

3.2.3 Two dimensional echo assessment

3.2.3.1 Assessment of left ventricular volumes and ejection fraction

Left ventricular volume and ejection fraction were calculated from the apical 4- and 2-chamber views using the Simpson's rule method (Figure 3.18).

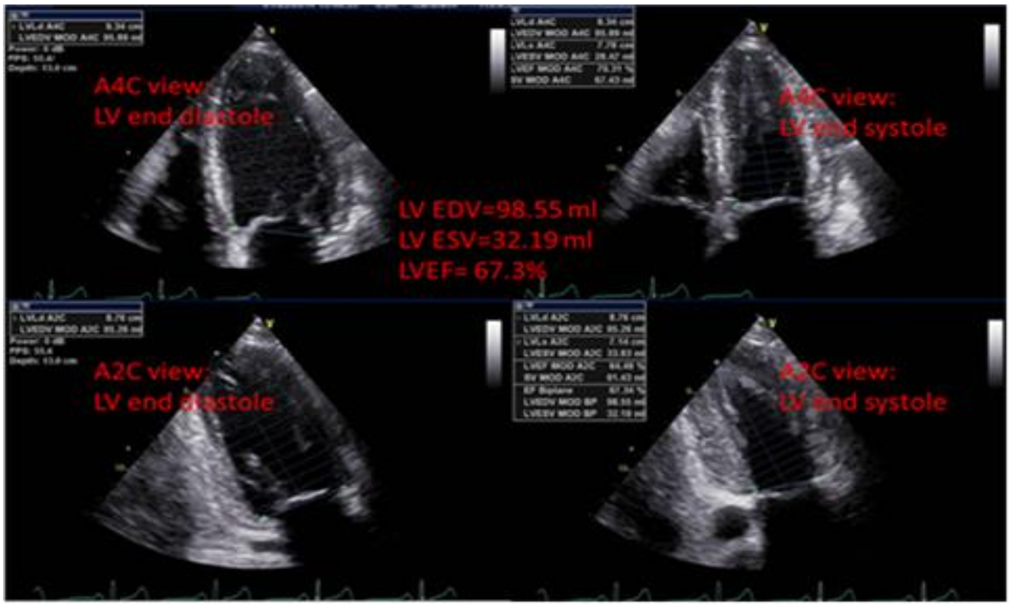


Figure 3.18 Measurement of LV volume (Modified Simpson's)

3.2.3.2. Assessment of left atrial volume

Left atrial volume was calculated from the apical 4- and 2-chamber views using the Simpson's rule method. LA enlargement (LAE) defined as LAVi≥34 ml/m^2 (Figure 3.19)[187].

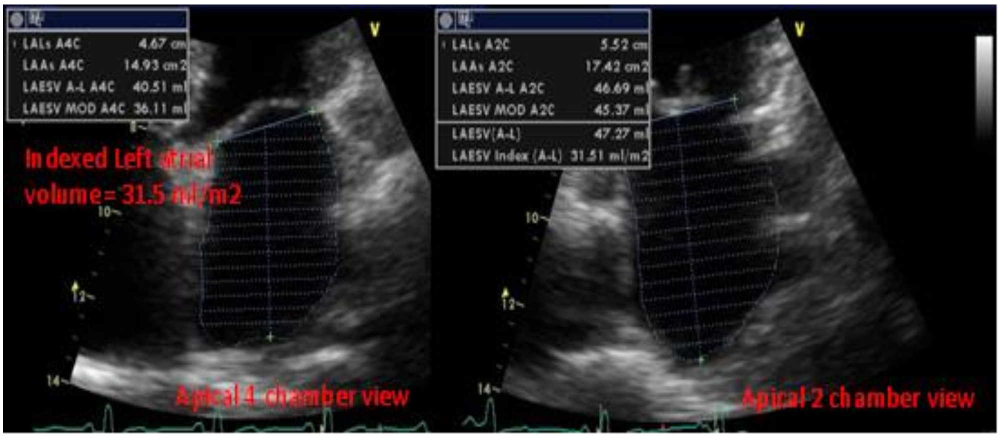


Figure 3.19 Measurement of left atrial volume

3.2.4 Standard Doppler assessment of diastolic function.

Mitral inflow peak early diastolic velocity (E), peak late diastolic velocity (A), E/A ratio, E wave deceleration time (DecT) were measured for diastolic function assessment. Tissue Doppler mitral annular early diastolic velocity (e') was assessed at septal and lateral annulus and averaged for calculation of E/e'; septal E/e'≥15, lateral

E/e'≥13 and averaged ≥14 were defined as abnormal[188]. Diastolic dysfunction (DD) grade was defined as previously described[189].

1) grade I Diastolic dysfunction: E/A <0.8, E/e'<10, pulmonary venous inflow S<D;

2) grade II DD: 0.8<E/A<1.5, E/e' > 10 or LAE, or presence of mid diastolic forward flow (L wave), or positive Valsalva (> 50% increased of E/A ratio);

3) grade III DD: E/A> 1.5, DecT<140 ms.

3.2.5 Speckle Tracking Echocardiography (STE)

Each segment of myocardium has its own unique speckle pattern. Once the region of interest is defined by the operator, imaging software tracks this speckle pattern frame by frame throughout the cardiac cycle[190]. As the tracking is based on grayscale B-mode imaging, it is principally angle independent (Figure 3.20)**.** Strain describes the deformation of the myocardium and is defined as change in length normalized to the original length (Figure 3.21) (Figure 3.22).

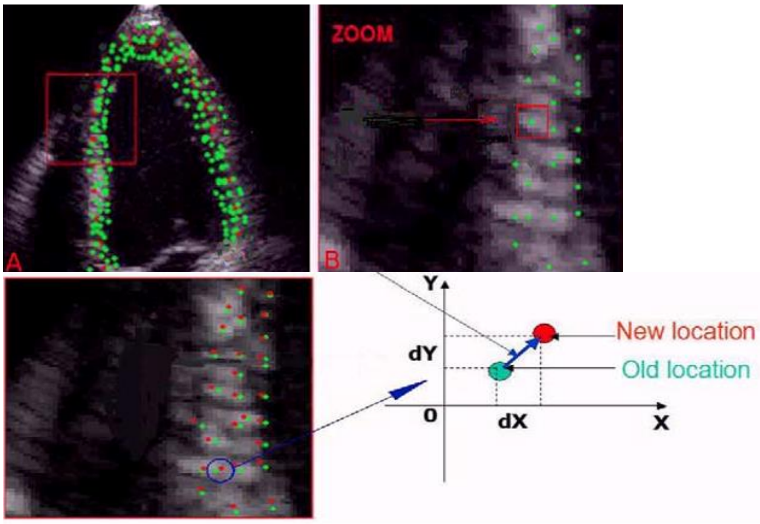
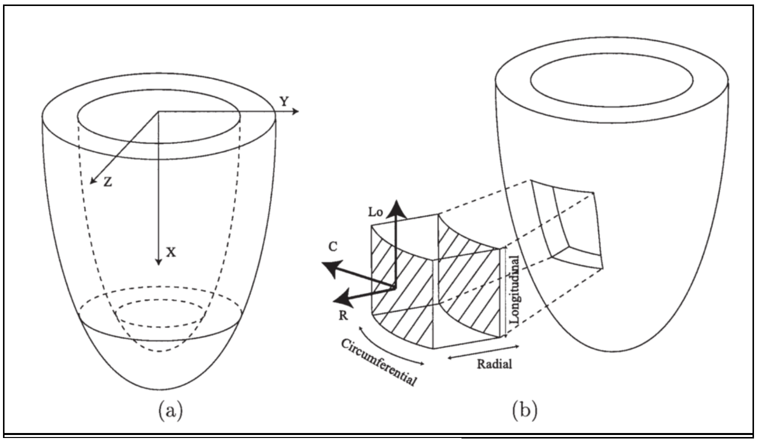


Figure 3.20 Speckle tracking echocardiography.
Modified from Leitman, J Am Soc Echocardiogr. 2004;17(10):1021-1029.



$$S = \frac{l - l_0}{l_0} = \frac{\Delta l}{l_0}$$

Figure 3.21 Measurement of strain
(Left) long/circumferential/radial axis. (Right) calculation of strain: l_0=initial length; l=instantaneous length.
Modified from D'Hooge J, Eur J Echocadiogr. 2000;1(3):154-170

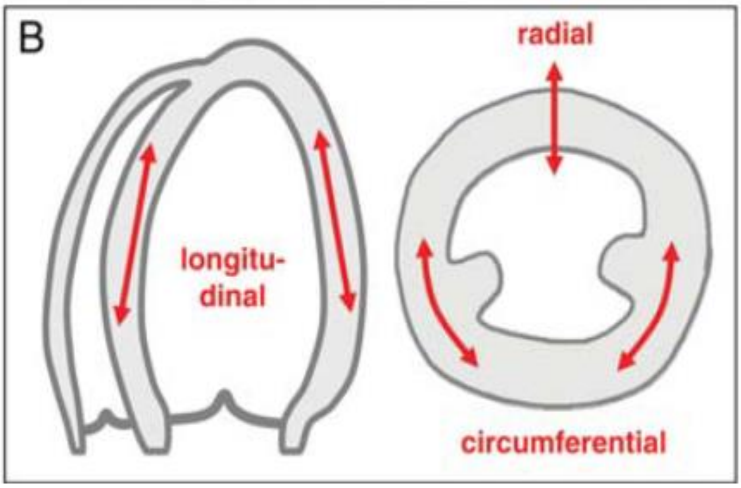


Figure 3.22 Measurement of strain from three imaging planes
(longitudinal, circumferential and radial dimension) speckle tracking and strain.
Adopted from Mor-Avi V et al. Eur J Echocardiogr. 2011;12(3):167-205.

Previous studies have demonstrated that this semi-automated imaging tool was highly feasible and reproducible[84,123]. The techniques used for this measurement followed standard methodology[191,192].

Left ventricular peak longitudinal strain measurements were obtained from grey scale-recorded images in the apical 4-chamber, 2-chamber and long-axis views. The endocardial border was manually traced in the end-systolic frame for each view, and the software subsequently traced the border in the other frames automatically. In the segments with poor tracking, the border was readjusted manually until adequate tracking was achieved. The cardiac cycle with the best tracking and visually most credible strain curves was selected for analysis[193].

Strain was analysed using velocity vector imaging (Syngo VVI, Siemens Medical Solutions) (Figure 3.23). GLS was measured on-line by averaging strain from the regional of interest in the apical 4-chamber, 2-chamber and long-axis views. Impaired GLS was defined using cut-off of <18 %[85,192]. Global circumferential strain (GCS) was measured off line. Global diastolic strain was obtained by averaging of all 18 segment strain values and measured according to method published by Ishii et.al[194].

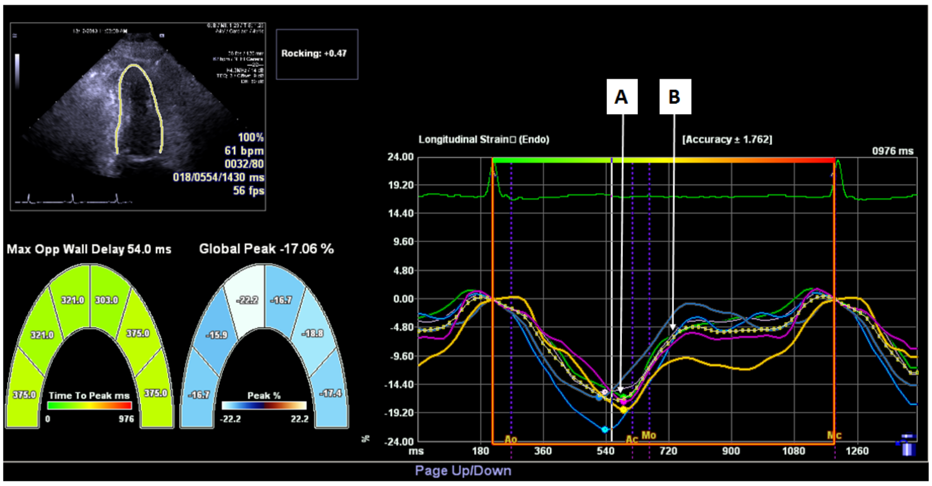


Figure 3.23 measurement of strain
Global longitudinal strain and diastolic strain in apical 2 chamber view

3.2.6 Three dimensional (3D) echocardiography assessment

Assessment of LVEF was also performed by acquiring a full- volume dataset using 4V1c probe and analysed using Syngo AVA proprietary software from Siemens. The 3-dimensional endocardial shell was constructed using semi-automated contour tracing. The resultant end-diastolic and end-systolic volumes were used to calculate 3D-left ventricular ejection fraction Figure 3.24.

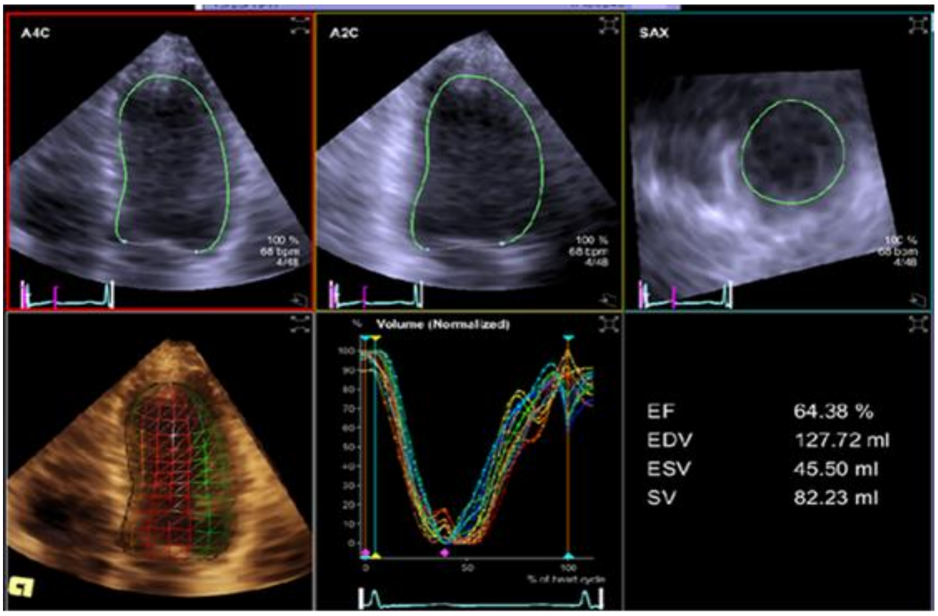


Figure 3.24 Three Dimensional echocardiography
Three dimensional echocardiography assessment of LV volumes (EDV, ESV) and ejection fraction (EF)

3.3 Standard Electrocardiogram

A standard 12-lead ECG was recorded at 25 mm/s and 1 mV/cm according to a standard protocol. ECG measurements were performed using MUSE software (GE Healthcare, Milwaukee, WI, 2USA) including QRS duration and axis, PR, QT and heart rate corrected QT intervals (QTc).

3.3.1 Cornell criteria and Sokolow-Lyon voltage

Cornell voltage (Cornell-V) was measured as $S_{V3}+R_{aVL}$ and criteria for LVH was defined as ≥2.8 mV (28 mm) in men and ≥2.0 mV (20 mm) in women[195]. Cornell product (Cornell-P) was measured as the product of QRS duration times Cornell voltage ($R_{aVL}+S_{V3}$, plus 6 mm in women), and criteria for LVH was defined as ≥ 2440 mm·ms[196]. Sokolow-Lyon voltage (SLV) was measured as $S_{V1}+R_{V5}$ or R_{V6}, and criteria for LVH was defined as≥ 3.5 mV (35mm)[197]. The 75th percentile of gender specific cut-offs for Cornell-V, SLV and Cornell-P from the current study population were also used as categorical cut-offs for analysis.

3.3.2 Minimal changes in the lateral leads

Digital 12-lead ECG tracings were analysed by computer at midpoint of the ST segment on median complexes in leads V5 and V6[198]. The maximal magnitude of ST deviation in these leads was measured. The cut-off for absolute ST segment deviation (minSTmV5V6, the midpoint of the ST segment on median complexes in leads V5 and V6) was defined as <-20uV.

3.3.3 P wave terminal force

Abnormal P-wave terminal force in the right precordial lead V1 (PTFV1)[199] was defined as the product of the negative P-wave deflection from onset of the negative deflection to its nadir in lead V1 [uV] and the duration [ms]) (Figure 3.25)**.** The cut-off used was defined as ≤ -4000 uVms.

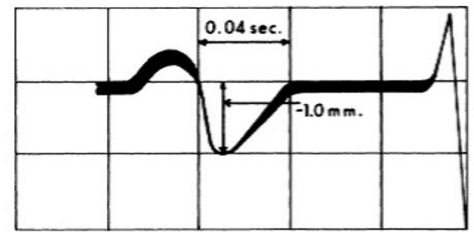


Figure 3.25 measurement of p wave terminal force

3.4 Standard Questionnaires

3.4.1 Duke Activity Status Index.

The Duke Activity Status Index (DASI) questionnaire is a self-assessment tool that was developed to predict an individual’s maximal exercise capacity [200]. It includes 12 activities representative of major aspects of physical function (personal care, ambulation, household tasks, sexual function, and recreational activities). A score is calculated based on weighted answers from 12 questions related to daily activities of living, for which each item is weighted by its known metabolic cost, and weights of positive terms are summed to form the individual patient DASI score. The possible scores range from 0 (“no” to all answers) to 58.2 (“yes” to all answers) with higher scores representing better functional activity. Estimated peak oxygen consumption was calculated according the original formula from Hlatky et al [200]:

Peak VO2 (in mL/kg/min) = 0.43xDASI score+9.6

Metabolic equivalent (MET) was calculated as 1MET=3.5 mL/kg/min.

3.4.2 EuroQol 5 Dimensions Index and Visual Analogue Scale.

The EuroQol 5 Dimensions Index (EQ-5D) and Visual Analogue Scale (EQ-VAS) [201] have been used to measure general health status in numerous patient populations, including patients with heart failure [202]. The EQ-5D descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The response for 5 dimensions can be combined in a 5-digit number which then translates to index-based values according to general population samples.

The index (utilities) ranged from 0-1, with higher numbers representing better health status. The EQVAS records the respondent's self-rated health on a vertical visual analogue scale from 0 (worst imaginable) to 100 (best imaginable).

3.4.3 Minnesota Living with Heart Failure Questionnaire (MLHFQ)

MLHFQ includes the most pertinent questions to assess the impact of frequent physical symptoms of HF - shortness of breath, fatigue, peripheral oedema, and difficulty sleeping, and psychological symptoms of anxiety and depression. It has 21 questions, each ranging from 0 (not at all) to 5 (very much).

The MLHF is scored from 0 to 105 with lower scores representing better health [203].

3.4.4 Anxiety and Depression scores (GAD-7) and PHQ-0

Generalized Anxiety Disorder-7 (GAD-7) and Patient Health Questionnaire-9 (PHQ9)

PHQ-9 is used for assessing and monitoring depression severity. It has nine items, each of which is scored 0 (not at all) to 3 (nearly every day), providing a 0 to 27 severity.

GAD-7 is an anxiety measure using 7 items, each of which is scored 0 (not at all) to 3 (nearly every day), providing a 0 to 21 severity score.

In general, cut points of 5, 10 and 15 represent mild, moderate and severe levels of depressive and anxiety symptoms on PHQ-9 and GAD-7, respectively [204].

3.4.5 SOF Frailty index.

The Study of Osteoporotic Fractures (SOF) frailty index [205] is a simple measure using 3 components [206]. The frailty status was defined as robust (0 components), pre-frail (1 component) and frail (2 or more components). This is a practical index, the performance of which is compatible with other frailty markers [207].

3.4.6 Charlson Comorbidity Score

Charlson Comorbidity Score is a weighted index that takes into account the number and the seriousness of comorbid disease[208]. This method of classifying comorbidity provides a simple, readily applicable and valid method of estimating risk of death from comorbid disease for use in longitudinal studies. The assigned weights was “1” for myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease and diabetes. The assigned weight was “2” for hemiplegia, moderate or severe renal disease, diabetes with end organ damage, any tumour, leukaemia and lymphoma. The assigned weight was “3” for moderate or severe liver disease and the assigned weight was “4” for metastatic solid tumour and AIDS[208].

3.5 Assessment of Functional Capacity - Six Minute Walk Test

The measurement of sub-maximum functional capacity in this study was a 6-minute walk test distance (6MW). 6MW, conducted following a standardized protocol [209]. A 25-meter flat, obstacle-free corridor, with visible markers at each meter interval and stop coins placed at either end, was used. Participants were instructed to walk as far as possible, turning 180̊ every 25 meters in the allotted time of 6 minutes. They were able to rest, if needed, and the time remaining was called out after every lap. The participant walked unaccompanied. Verbal encouragement was given to participants. At the end of 6 minutes, they were instructed to stop and the total distance covered was measured to the nearest meter.

Functional capacity can be estimated using Metabolic Equivalents (METS) from the 6MW distance using a validated formula by Ross et al [210]) as follows:

Mean Peak VO2 (ml/kg/min) =4.948+0.023*Mean 6MW distances (meters)

In terms of relating to age and gender specific cut-offs of metabolic equivalents (METs) for normal male[211] and female[212], the following formulae were used in this thesis:

For Male: METs=18.0-(0.15*age)

For female: METs=14.7-(0.13*age)

Postscript

In this chapter, we have documented the methodology used in these studies. LV strain has a central role. So the next chapter will discuss one the most important issues of using strain in routine clinical management – measurement variability. So far, measurement variability between vendors has been documented in the literature as one of the most important limitations of this new metric. However, with the effort of a joint task force of The European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE) in 2011, it may be that standardization has had sufficient effect to make strain a standard measurement.

Appendix (the questionnaires)

Duke Activity Status Index

The DASI Patient Questionnaire

The Duke Activity Status Index has been removed for copyright reasons

EuroQol 5 Dimensions Index

EQ-5D Health Questionnaire

The EuroQol 5 Dimensions Index has been removed for copyright reasons

EuroQol5 Visual Analogue Scale

Minnesota Living with Heart Failure Questionnaire (MLHFQ)

MINNESOTA LIVING WITH HEART FAILURE© QUESTIONNAIRE

The Minnesota Living with Heart Failure Questionnaire (MLHFQ) has been removed for copyright reasons

Generalized Anxiety score (GAD7)

The Generalized Anxiety score (GAD7) has been removed for copyright reasons

Patient Health Questionnaire-9 (PHQ9)

The Patient Health Questionnaire-9 (PHQ9) has been removed for copyright reasons

SOF frailty index

The SOF frailty index has been removed for copyright reasons

Charlson Comorbidity Score

The Charlson Comorbidity Score has been removed for copyright reasons

Chapter 4

Use of Strain for Screening – Is it Robust Enough?

Article “Improvement in Strain Concordance between Two Major Vendors after the Strain Standardization Initiative” was published in

Journal of American Society of Echocardiography 2015;28(6):642-8

Yang H, Marwick TH, Fukuda N, Oe H, Saito M, Thomas JD, Negishi K

Chapter 4. Use of Strain for Screening – is it Robust Enough?

Introduction

One of the most important aspects of this research is to show the benefit of imaging surveillance in the community. In the attempt to compare the feasibility and effectiveness of advanced imaging (speckle tracking echocardiography and diastology) versus conventional imaging (left ventricular ejection fraction) in the community, this chapter addresses the important issue of measurement variability of speckle tracking.

The conventional echocardiographic assessment of left ventricular ejection fraction and diastolic functional assessment has been widely used in routine clinical practice regardless of their load and operator dependency. Strain is a more sensitive marker and semi-automated technique. However, the measurement variability between vendors is potentially a major limitation and of concern in our community based trial. It is therefore important to assess whether this issue has been improved with the current versions of analysis software and whether the current strain measurement variability is acceptable and equivalent compared with that of left ventricular ejection fraction.

The following text in this chapter has been published in the ***Journal of American Society of Echocardiography. JASE 2015; 28 (6):642-8***

Abstract

Background: Disagreement of strain measurements among different vendors has provided an obstacle to the clinical use of strain. A joint standardization task force between professional societies and industry was initiated to reduce inter-vendor variability of strain. Although feedback from this process has been used in software upgrades, little is known about the effects of efforts to improve conformity. We sought whether inter-vendor agreement for global longitudinal strain (GLS) has improved after standardization initiatives.

Methods: Eighty-two subjects (52±21years, 55% male) prospectively underwent two sequential examinations using two most common ultrasound systems (Vivid E9 vs. iE33). GLS was calculated using proprietary software EchoPAC BT12 (E12) and BT13 (E13) versus QLAB 8 (Q8), QLAB 9 (Q9) and QLAB 10 (Q10). Agreements in GLS were evaluated with Bland-Altman plots. Coefficients of variation (CVs) were compared using Friedman test and compared with CVs of LV volumes and ejection fraction (EF).

Results: Median GLS using E12 was -19.2% (inter-quartile range: -15.2%, -23.2%), compared with -19.3% (IQR -14.9%, -23.7%) for E13, -15.7% (-11.4%, -20%) for Q8, -19% (-15.7%, -22.3%) for Q9 and -18.7% (-15.7%, -21.7%) for Q10. The CVs of pre-standardization GLS (12±8% [E12/Q8]; 14±8 [E13/Q8]) were significantly larger than EF (5±5) ($p<0.001$). After standardization, the CVs of GLS have shown improvement (6±4) [E12/Q9]; 7±4 [E12/Q10]; 6±4 [E13/ Q9]; 7±4 [E13/Q10]) and are similar to those of EF.

Conclusions: Subsequent to the joint standardization task force, there has been improvement in between-vendor concordance in GLS between two leading ultrasound manufactures, the variability of which is now analogous to that of LVEF. The removal of concerns about measurement variability should allow wider use of GLS.

4.1 Background

Measurement of strain using two dimensional speckle tracking echocardiography (STE) is a relatively new test for the assessment of cardiac function, especially for the quantitative evaluation of global and regional myocardial function [213]. STE has largely replaced tissue Doppler derived strain, due to reduction of angle- and operator-dependence, and STE has become an integrated application in most commercially available ultrasound systems. However, variations in proprietary software among vendors - causing poor inter-vendor agreement in measurements – have become a significant limitation on the implementation of STE [86,193,214-217]. This limitation has raised the concern of STE becoming an acceptable mainstream methodology in daily clinical application, especially in laboratories with echocardiographic instruments from multiple vendors. In order to achieve a consensus on methodology for the quantitative evaluation of cardiac mechanics, the European Association of

Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE) invited vendors to participate in a concerted effort to reduce inter-vendor variability of strain measurement[213,218,219]. Guidance has been provided about the steps necessary to reduce variability, and this information has been used in software upgrades, but little is known about the effects of this process.

4.2 Aim and Objectives

The aim of this study was to elucidate whether there is an improvement in inter-vendor global strain (GLS) agreement using STE after the implementation of standardization initiatives. Despite variabilities of LV volumes and ejection fraction (EF) measurements, these are used clinically for serial evaluation, so variations in these parameters were used as a frame of reference to compare variations in GLS.

4.3 Material and Methods

Study population. Adult participants who had clinically indicated echocardiography were prospectively recruited in outpatient clinic in Royal Hobart Hospital, Australia and Takasaki General Medical Centre, Japan from June 2013 to November 2013. A group of adult healthy volunteers was also included in the study. We included patients of age >18 years, without atrial fibrillation or flutter. All subjects underwent two transthoracic echocardiograms using two ultrasound systems by the same experienced sonographers. The study protocol was approved by the relevant Institutional Review Boards[220].

Standard echocardiography. Transthoracic echocardiograms were performed using commercially available ultrasound systems from two vendors (S5-1 probe, iE33, Philips, Andover, MA, USA; M5S probe, Vivid E9 and M4S probe, Vivid 7 Dimension, GE Medical, and Milwaukee, WI, USA). Each participant first underwent an extensive standard assessment of cardiac anatomy and cardiac function according to clinical protocol with one ultrasound system. This was repeated using the other ultrasound system. Acquisition was obtained at the highest possible frame rate with optimization of image depth and sector width. Multiple consecutive cardiac cycles of the three standard apical views (A4C, A2C and ALAX views) were acquired and digitally stored as raw data for offline analysis. LV end-diastolic and end-systolic volumes were performed using the biplane method of disks [221]. The baseline assessment included standard 2D, M-mode, color Doppler, pulse wave and continuous wave Doppler and tissue Doppler imaging modalities using standard parasternal, apical, subcostal and suprasternal windows.

Measurement of myocardial strain. Measurement of GLS has been previously described [193]. Briefly, 2-dimensional images from 3 apical views (A4C, A2C and ALAX views) were used. Readings were obtained by averaging 6 segments in each view. GLS was determined from the average of all 18 segments. Figure 3.1 is a schematic description of image acquisition, strain analyses and comparisons using the respective three generations of proprietary software packages from the two vendors. In the images acquired on Vivid E9 (Figure 4.26A), speckle tracking analyses were performed using proprietary software (EchoPAC-PC BT12 [E12, released March 2012] and BT13 [E13, released May 2013], GE Medical, Milwaukee, WI). After tracing of the endocardial border, the region of interest was adjusted to include the entire myocardial thickness and avoid the pericardium. The software then selected stable speckles within the myocardium and performed speckle tracking on a frame-to-frame basis throughout the entire cardiac cycle. The adequacy of tracking was verified manually. The cardiac cycle with the best tracking and visually most credible strain curves was selected for analysis. In segments with poor tracking, the border was readjusted manually until optimal tracking was achieved. After adjustment, segments with consistently poor tracking were excluded. Final GLS was calculated as the averaged value of GLSs from each apical view, using peak negative longitudinal strain during the cardiac cycle.

Since EchoPAC BT11 (E11, released May 2010) cannot analyze the images acquired using current Vivid E9 due to lack of compatibility with older versions of software, a separate group of normal volunteers was imaged using GE Vivid 7 Dimension (frame rate 72±6 Hz) only for the comparison of E11 and E12 (Figure 4.26B). All offline measurement with E11, E12 and E13 was performed by a single observer (HY).

Images acquired on the iE33 were analyzed using proprietary software from before the standardization initiative (QLAB version 8.0 [Q8], released April 2010) and after the standardization initiative (QLAB version 9.0 [Q9], released February 2012 and version 10.0 [Q10], released August 2013, Philips Medical, Andover, MA). For each view, endocardial and epicardial borders were manually traced in the end-systolic frame using three software versions with the same image view. All three software versions were used to trace the borders automatically frame-by-frame throughout the same cardiac cycle. Visual inspection of the tracking was carefully performed, and if automated tracking was unsatisfactory, manual point-to-point and frame-to-frame adjustments were carefully made until satisfactory tracking was achieved. Electrocardiographic tracing was used to estimate the timing of end-systole and early diastole. All offline measurement with QLAB was performed by the same observer (HY). The analyses using QLAB were performed 4 weeks after analysis of EchoPAC, and the operator was blinded to the previous measurements.

Statistical Analysis. Continuous variables are presented as mean ± standard deviation (SD). Categorical variables are expressed as percentages. Normality was evaluated using the Shapiro-Wilk W-test. As strain was not normally distributed, Spearman's rho was used to express correlation coefficient. The agreements between two vendors and with two software versions were studied using Bland-Altman analysis[222] to quantify a systemic difference (bias) between two techniques and the spread of differences of mean bias (limits of agreement [LOA]). Intraclass correlation coefficients (ICCs) were also used for the assessment of agreement. The coefficient of variation (CV) was calculated for all measurements. The difference of each paired variables was also assessed by percentage error. Percentage error was derived by dividing the limits of agreement divided by the mean[223]. The CV of different systems among four series of parameters (LV end-diastolic volume [LVEDV], end-systolic volume [LVESV], LVEF and GLS) were compared using Friedman test, followed by pairwise tests with Bonferroni' s correction.

To assess intra-observer variability, the same operator performed measurements after an interval of at least two weeks in 20 randomly selected subjects, blinded to previous measurements. For the assessment of inter observer variability, a second operator (KN) blindly measured the same group of subjects. Intra-observer and inter-observer variability values were summarized as the absolute difference, CV, ICC and Bland-Altman statistics and by calculating the coefficients of variation.

Statistical analysis was performed using IBM SPSS statistics (version 20, IBM Corp., Armonk, NY, USA) and MedCalc version 12.0.1.0 (MedCalc Software, Mariakerke, Belgium). Statistical significance was accepted at a P value of <0.05.

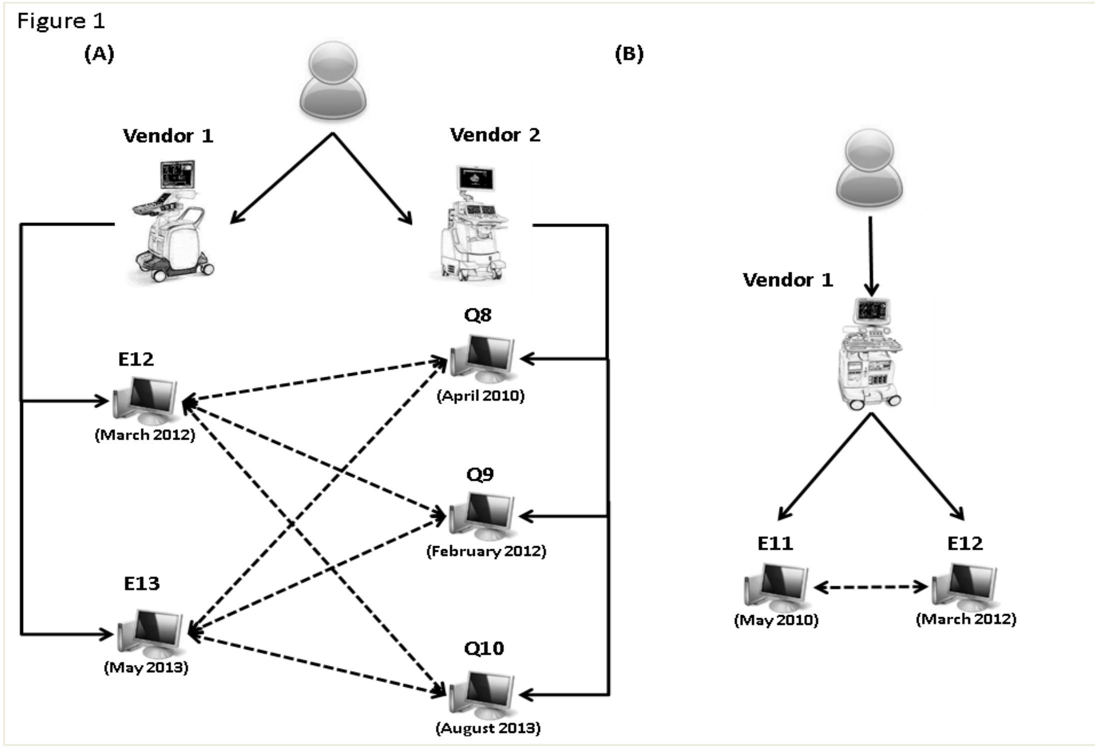


Figure 4.26 Schematic description
Schematic description of Ultrasound systems, software versions and combinations of comparisons
A) In the between vendor comparisons, echocardiographic images were acquired with two ultrasound systems for each patient. The images were analyzed with vendor specific software versions (E12 and E13 for Vivid E9; Q8, Q9 and Q10 for iE33).
B) A separate group of normal volunteers was imaged using GE Vivid 7 and analyzed and compared using E11 and E12. Software release dates were shown in the brackets.
E11 (EchoPAC version BT11); E12 (EchoPAC version BT12); E13 (EchoPAC version BT13); Q10 (QLAB version 10); Q9 (QLAB version 9); Q8 (QLAB version 8)

4.4 Results

Characteristics of study population. Two patients were excluded at time of image acquisition due to inadequate and suboptimal image quality, a total of 82 subjects (45 men, 55%) were included in the main comparison between the vendors (Figure 4.26A)**.**

Their baseline demographics, conventional echocardiographic parameters and indications for echocardiography are summarized in Table 4.21. Among them, 16 (20%) were healthy volunteers who were free of clinical symptoms and signs. The study population had wide ranges of age (18-95, mean 52±20.3 years) and body mass index (16-43, mean 25±6 kg/m^2). Their LVEF was 58±12 % (14-72%). Frame rate of images acquired by iE33 (60±6 Hz) were significantly higher ($p<0.001$) than those acquired by Vivid E9 (56±6 Hz).

Measurement of GLS using various software versions. The measurement of GLS was feasible with each software version in all cases. The median values of GLS using E12 was -19.2% (inter-quartile range [IQR]: -15.2% to -23.2%), compared with -19.3% (IQR -14.9% to -23.7%) for E13, -15.7% (IQR: -11.4% to -20%) for Q8, -19% (IQR: -15.7% to -22.3%) for Q9 and -18.7% (IQR: -15.7% to -21.7%) for Q10. These were summarized in Table appendix 4.24**.** Overall, GLS showed a good correlation between EchoPAC versions (E12 and E13) and QLAB versions (Q8; Q9 and Q10). However, the bias and LOA were greater between E12 and E13 versus Q8 than between E12 and E13 versus Q9 and Q10 (Table 4.22 and Figure appendix 4.29 to Figure appendix 4.32).

Table 4.21 Clinical and Echo characteristics

Clinical Characteristics	N=82
Age, y	52±20.6
Male, n (%)	45(55)
Weight, kg	71±19
Height, cm	166±11
Body mass index (BMI), kg/m^2	25±6
Body surface area (BSA), m^2	1.78±0.25
Systolic blood pressure (mmHg)	128±21
Diastolic blood pressure (mmHg)	72±15
Heart rate (beats/min)	67±11
Echocardiographic data	
LVEDV (ml/m^2)	54±23
LVESV (ml/m^2)	25±20
LVSV (ml/m^2)	29±7
LVEF (%)	58±12
Left atrium volume (ml/m^2)	30±11
Deceleration time (ms)	204±58
E/A	1.24±0.64
e'	0.08±0.04
E/e'	10.3±6.6
Indications for echocardiography	**n (%)**
Ischemic heart disease	11 (13.4)
Arrhythmia	10 (12.2)
Heart murmur	7 (8.5)
Shortness of breath	9 (11.0)
Heart failure	8 (9.8)
Cardiomyopathy	7 (8.5)
Pericarditis	2 (2.4)
Post Chemotherapy	3 (3.7)
Systemic disease	4 (4.9)
Miscellaneous	5 (6.1)
Normal Volunteer	16 (19.5)

Results of GLS between Q9 (post-standardization) and Q8 (pre-standardization) showed association but significant difference (rho=0.68; bias=-2.6%; LOA=5.0%). A similar result was observed comparing Q10 (post-standardization) with Q8 (rho=0.67; bias=2.2%; LOA=4.9%). Good correlation was observed comparing E12 versus E13 (rho=0.94; bias=0.1%; LOA=2.0%) and Q9 versus Q10 (rho=0.90; bias=0.4%; LOA=2.5%), both were developed after the standardization task force (Table 4.22 and Figure appendix 4.29 to Figure appendix 4.32).

Table 4.22 Analyses of variation between variables

Variables	ICC (95% CI)	Rho	Bias	LOA	Percentage error
LVEDV (GE/Philip) (ml)	0.96 (0.93-0.97)	0.79	-6.4	33.8	0.39±0.12
LVESV (GE/Philip) (ml)	0.98 (0.96-0.98)	0.77	-2.9	22.8	0.68±0.29
LVEF (GE/Philip)	0.95 (0.93-0.97)	0.79	-0.1	9.8	0.18±0.08
GLS (E12_Q8) (%)	0.79 (0.67-0.86)	0.81	-2.7	4.5	-0.28±0.14
GLS (E13_Q8) (%)	0.78 (0.65-0.86)	0.81	-2.8	4.5	-0.29±0.11
GLS (E12_Q9) (%)	0.91 (0.86-0.94)	0.81	-0.2	3.5	-0.21±0.08
GLS (E13_Q9) (%)	0.95 (0.92-0.97)	0.78	-0.2	3.7	-0.22±0.09
GLS (E12_Q10) (%)	0.95 (0.92-0.97)	0.76	-0.5	3.5	-0.22±0.09
GLS (E13_Q10) (%)	0.94 (0.91-0.96)	0.74	-0.6	3.7	-0.23±0.09
GLS (E13_E12) (%)	0.99 (0.98-0.99)	0.94	0.1	2.0	-0.12±0.05
GLS (Q9_Q10) (%)	0.97 (0.96-0.98)	0.90	0.4	2.5	-0.15±0.06
GLS (Q9_Q8) (%)	0.75 (0.61-0.84)	0.68	-2.6	5.0	-0.33±0.12
GLS (Q10_Q8) (%)	0.80 (0.68-0.87)	0.67	2.2	4.9	-0.32±0.12
GLS* (E11_E12) (%)	0.94 (0.91-0.96)	0.89	0.1	2.0	-0.098±0.01

LVEDV (End-diastolic volume); LVESV (End-systolic volume); LVEF (Left ventricular ejection fraction); GLS (Global longitudinal strain); CV (coefficient of variation); SD (standard deviation); LOA (Limits of agreement); ICC (Intraclass correlation); E12 (EchoPAC version BT12); E13 (EchoPAC version BT13); Q10 (QLAB version 10); Q9 (QLAB version 9); Q8 (QLAB version 8)
*A separate group of normal volunteers (n=76) comparing between E11 and E12 only

GLS was also analyzed and compared using E11 and E12 in a separate group of normal volunteers (n=76) **(**Figure 4.26**).** The comparability of E11 and E12 showed good correlation (rho=0.883; bias=0.1%; LOA=2.0%; Figure 4.26B). The coefficient of variance between E11 and E12 was -0.03±0.02, ICC was 0.94 (0.91-0.96).

Comparison between GLS and LV volumes. Using the Vivid E9, the mean LVEDV (95±41 ml), LVESV (43±35 ml) and EF (58.0±11.8%), were largely similar compared with those obtained using iE33 (102±48ml, 46±41 ml and 58.1%±11.9%, respectively). (Table appendix 4.24). The CV and percentage error of LVEDV, LVESV and LVEF between the two machines are summarized in Table 4.22. Using the Friedman Test with Bonferroni correction, the CV of LVEF were significantly different from that of LVEDV ($p<0.001$) and LVESV ($p<0.001$). The CV of LVEDV and LVESV showed no significant difference.

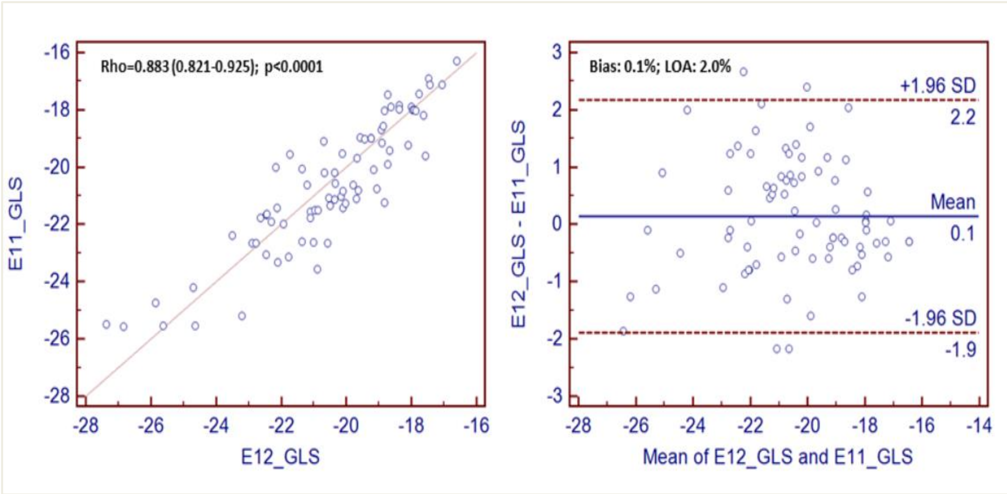


Figure 4.27 Scatter and Bland-Altman Plots
The comparison between E11 and E12. Left: Scatter plot. Right: Bland-Altman plot.

The CVs of pre-standardization GLS (0.12±0.08 [E12 versus Q8]; 0.14±0.08 [E13 versus Q8]) were significantly larger than LVEF (0.05±0.05) ($p<0.001$). Since standardization, the CVs of GLS have shown improvement (0.06±0.04) [E12 versus Q9]; 0.07±0.04 [E12 versus Q10]; 0.06±0.04 [E13 versus Q9]; 0.07±0.04 [E13 versus Q10]). There was no significant difference in the CV of differences in LVEF and that of GLS using post-standardization software; E12 versus Q9 ($p=0.99$); E13 versus Q9 ($p=0.81$); E12 versus Q10 ($p=0.22$) and E13 versus Q10 ($p=0.091$) (Figure 4.28a, and Table appendix 4.25). Figure 4.28b describes comparison of CVs of within vendor software versions (Q8 versus Q9; Q8 versus Q10; Q9 versus Q10 and E12 versus E13) to CV of LVEF.

Intraobserver and interobserver variability. The intra-observer and inter-observer variability of GLS from E12, E13, Q8, Q9 and Q10 were acceptable (Table 4.23). There were no significant differences among the CVs in intra- ($p=0.96$) and inter- ($p=0.11$) observer variabilities.

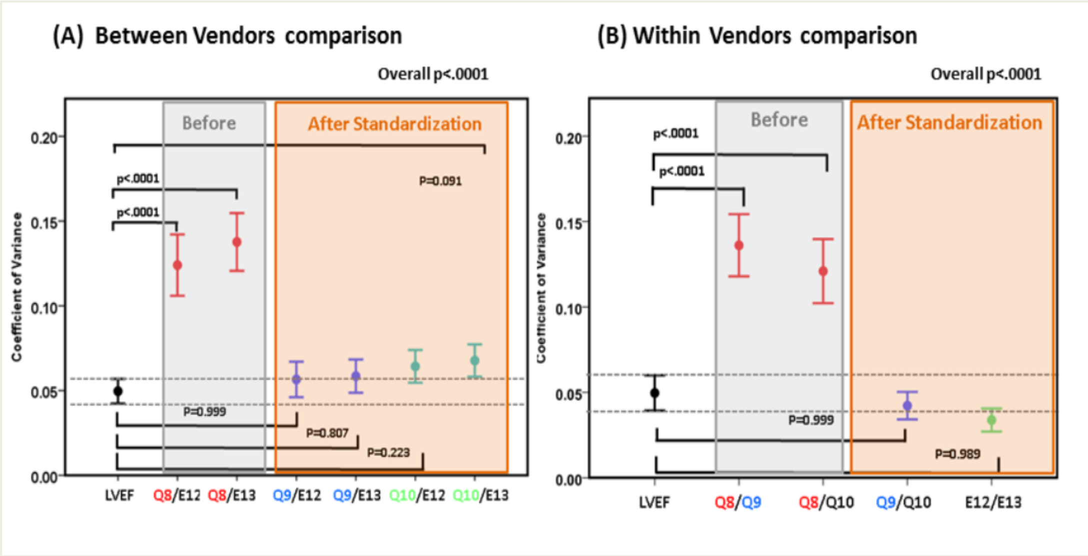


Figure 4.28 Comparison of coefficient of variance

A): Comparisons among the coefficients of variance (CVs) from LVEF and between vendor software comparisons of GLS (Q8 versus E12, Q8 versus E13, Q9 versus E12, Q9 versus E13, Q10 versus E12, Q10 versus E13) Software before standardization: Q8; software after standardization: Q9, Q10, E12, and E13.

B): Comparisons among the CVs of LVEF and within vendor software comparisons of GLS (Q8 versus Q9, Q8 versus Q10, Q9 versus Q10, E12 versus E13).

Table 4.23 Reproducibility Analysis

Versions	Intraobserver reproducibility			
	Absolute Mean difference (%)	CV (SD)	ICC (95% CI)	Bias (LOA) %
E12	0.08±1.03	-0.03±0.03	0.98 (0.97-0.99)	0.10 (2.0)
E13	-0.09±0.71	-0.02±0.02	0.99 (0.986-0.997)	-0.09 (1.4)
Q8	-0.19±0.71	-0.03±0.02	0.99 (0.98-0.99)	-0.20 (1.3)
Q9	0.37±1.16	-0.04±0.04	0.98 (0.96-0.99)	0.40 (2.3)
Q10	0.20±0.72	-0.03±0.02	0.99 (0.98-0.99)	0.20 (2.1)
	Interobserver reproducibility			
	Absolute Mean Difference (%)	CV	ICC (95% CI)	Bias (LOA)%
E12	0.41±1.36	-0.04±0.03	0.98 (0.94-0.99)	0.4 (2.6)
E13	0.40±0.82	-0.04±0.02	0.99 (0.988-0.998)	-0.3(1.1)
Q8	-0.52±0.7	-0.04±0.03	0.99 (0.94-0.99)	-0.5 (1.3)
Q9	-0.27±2.27	-0.08±0.07	0.94 (0.85-0.98)	-0.3 (4.4)
Q10	0.55±1.30	-0.05±0.05	0.96 (0.91-0.99)	-0.7 (2.9)

GLS (Global longitudinal strain); CV (coefficient of variation); ICC (Intraclass correlation); LOA (Limits of agreement); E12 (EchoPAC BT12); E13 (EchoPAC BT13); Q8 (QLAB version 8); Q9 (QLAB version 9); Q10 (QLAB version 10)

4.5 Discussion

Between-vendor variability is often cited as a limitation of the clinical application of strain imaging. The results of this study demonstrate a reduction of variability of GLS in earlier- and later-developed software versions between two leading ultrasound manufactures, perhaps reflecting the implementation of the consensus process. This improvement has made the between-vendor variability of GLS test analogous to that of LVEF, which we accept on a daily basis in the clinical setting.

Improvement of discordance of strain measurement among vendors. Agreements in GLS from different vendors in the literature have been controversial. Some reported they are similar[224-226], while others have demonstrated a difference [193,214,217,227-229] (Table appendix 4.26). The potential sources of variation in strain measurement are from image acquisition, post-processing and hemodynamic status of patients[86]. However, it appears that the predominant source of variation is differences between proprietary software [214,216,217,224]. Among different types of software, there are many differences in post-processing and strain algorithms, including the level of post-processed images that are used for strain calculation (radio-frequency vs post-processed data), the location of the region of interest (ROI, endocardial vs myocardial tracking), degree of smoothing, and details of strain processing including arithmetic, geographical or Gaussian averaging. The use of vendor independent software may be a solution in a multi-vendor laboratory [193]. However, this is not always clinically feasible, especially for immediate, online measurement.

Although all ultrasound vendors offer a means of measuring GLS, we sought to compare the most widely available. One of the used systems and proprietary software in the present study dominates the list of most commonly used vendors and techniques for STE analysis in the literature. In a meta-analysis of 24 studies on normal ranges of strain[85], 20 studies (83%) used this system and its proprietary software, and this system was a comparator in 11 of 12 (92%) of published studies comparing vendor discordance (Table appendix 4.26). This demonstration of an improvement in the concordance is relevant to clinical practice, being based on groups with a wide variety of diagnostic characteristics.

The temporal evolution of strain software. The change of concordance of software over time is the most important message of this paper. This was achieved through step by step multiple comparisons between and within vendors. Proprietary software produced by one vendor, E11 (a pre-standardization version) performed comparatively well with E12 (a post-standardization version), although this comparison needed a separate data set due to technical issues. This concordance was maintained in the main data set between E12 and E13 (another post-standardization and most updated version). These data support within-vendor concordance (E11, E12 and E13 versions), which is reassuring for the strain literature, as this vendor has provided the most widely used proprietary STE technology over the last 10 years. The concordance process has aligned the results of Q10 and E12, with the between-vendor differences becoming analogous to differences for standard echocardiographic parameters (Table appendix 4.26). However, this alignment has been achieved by changes between measurements obtained with Q8 (a pre-standardization version), Q9 (a post-standardization version) and Q10 (also a post-standardization and most updated version) – with the latter two being analogous. No previous studies have reported this comparison of software across time. It seems likely that this achievement of convergence over time is reflective of the effort of the joint task force.

Variability in volume measurement as compared to strain. Volume measurements using the biplane method of disks are recommended as a standard method for LV volume quantification by the American Society of Echocardiography (ASE)'s Guidelines and Standards Committee[221]. However, while left ventricular ejection fraction (LVEF) is an important predictor of outcome, and is widely used to monitor cardiac systolic function, this measurement has important technical limitations[230], as well as wide confidence intervals [231] that compromise its ability to detect subtle alterations in LV function.

The identification of the contour of the ventricle and its direction of contraction are fundamental to volumetric calculations, and analogous to the importance of endocardial tracking in speckle tracking analysis. The common limitations of these methods include: 1) geometric assumptions regarding the LV; 2) the impact of endocardial dropout; 3) inaccuracy due to foreshortening of the apex. These factors are inherent and accepted causes of variations in LV assessment, especially for serial follow-up studies. The finding that inter-vendor differences of GLS are analogous to

LVEF and less than volume assessment is an important step in the adoption of GLS into a routine clinical setting. These results are consistent with a successful outcome from the consensus process of EACVI, ASE and industry initiated in 2010, at least in the case of two widely-used vendors [219].

The study population is a strength of this study. To our knowledge, it is the largest data set using two ultrasound systems side by side, with wide range of age (18-95), BMI (16-43), left ventricular systolic function (EF 14-72), with both normal subjects and patients with various cardiac diseases. This approach does provide the limitation of comparing measurement on different echo cine clips, with physiological beat to beat variation in preload and afterload. Nonetheless, this variation is small (the CV of heart rate of the paired beats from the two systems was 0.05). Moreover, the variation in EF and volumes (which is a control for this process) was not less than that observed for strain.

Including a wide range of LV function has represented most clinical scenarios. Paradoxically, this comparison has provided the most favorable scenario – a wide range of contractile function yields higher correlation coefficients than a population of normal subjects only, and the variation might be smaller relative to the higher levels of strain.

4.6 Study Limitation

The main limitation of this study was that we evaluated the agreement among different version of software using the images from two widely-used vendor systems, thus our results cannot extrapolate to other versions/vendor systems. However, these systems are widely used in the literature. We had to use a separate dataset to evaluate the concordance among E11, E12 and E13 due to software version incompatibility. Although some may argue the use of the images acquired with previous generation system for entire comparisons, it does not reflect current concordance status because of lower image quality. Another point is to acknowledge that other relevant STE measurements were not analyzed in this study. These include global radial strain (GRS), global circumferential strain (GCS), twist/torsion as well as systolic and diastolic strain rate - some of which were achievable from conventional views. We performed analysis with GCS (data not shown) and found the overall CVs and biases were larger and ICCs and correlation coefficients were lower. As stated by EACVI and ASE's task force [219], our current clinical experience with GCS and GRS are limited as compared to GLS. Therefore, the standardization of these measures will await success in GLS standardization. Thus, our results should not be extrapolated to other parameters than longitudinal strain.

Improvements in overall image quality and product features are the source of consistent effort by all ultrasound manufacturers. As it is difficult to quantify these improvements over time for all vendors, we chose the two most widely used ultrasound systems in our current study. Although many users might feel that one vendor has changed more than the other, the exact changes by each manufacturer are difficult to obtain. Our results cannot be directly extrapolated to other vendor systems and software versions.

4.7 Conclusions

Robust and quantitative information is obtainable with global longitudinal strain. There has been an improvement in between-vendor concordance in GLS after the work of the joint standardization task force. This effort has made the variability of this test analogous with that of EF. The removal of concerns about measurement variability should allow wider use of GLS.

Postscript

This chapter has documented the robustness of our main assessment tool, GLS. Another important aspect is the role of experience and training in GLS measurement precision and validity. Negishi et al have extensively studied this in a recent study[349]. They found that interobserver agreement of GLS is better than LV ejection fraction by multiple observers. They also found that although experience is important, training appears to be of more value in assessment of segmental strain. The precision of GLS was high for all groups. Their finding further ensures the robustness of GLS measurement.

The following chapters will present studies that used data from Tasmanian Study of Echocardiographic Detection of Left Ventricular Dysfunction (TasELF) trial.

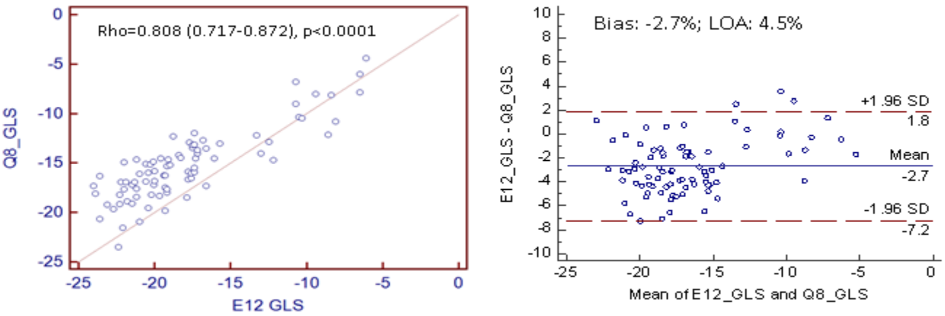
Although echocardiography is required to define stage B heart failure, there are several other methods that are more feasible and less costly, and potentially can be used as initial screening steps before echocardiography. **Chapter 7** address the role of ECG in its association with echocardiographic features and outcome. **Chapter 8** addresses a screening strategy using combined clinical risk scores, functional capacity and ECG. **Chapter 9** examines the role of individual echocardiographic marker and markers in combination in predicting new heart failure. **Chapter 6** is a cross-sectional analysis to examine and understand the two most commonly prevalent non-ischemic risk factors – diabetes and hypertension and their association with features of stage B heart failure. **Chapter 10** examines the intervention response to screening results as randomized control trial.

Another important risk factor is obesity. Overweight and obesity are highly prevalent in the community, even in a much younger age group. The next chapter will discuss whether childhood adiposity was related to adult cardiac dysfunction, i.e. should this have been used as one of our risk factors in screening?

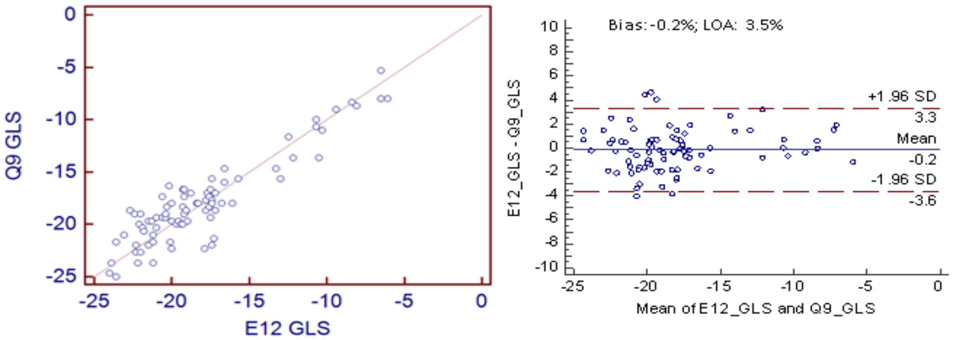
Appendix Figures and tables

Figure appendix 4.29 -comparison between vendor

A). E12 vs Q8



B). E12 vs Q9



C). E12 vs Q10

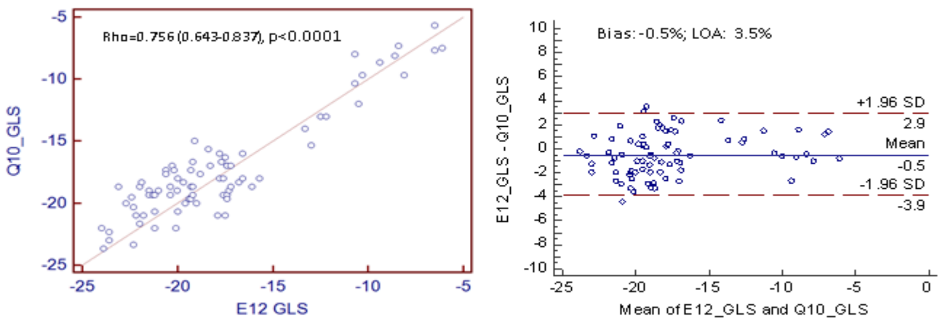
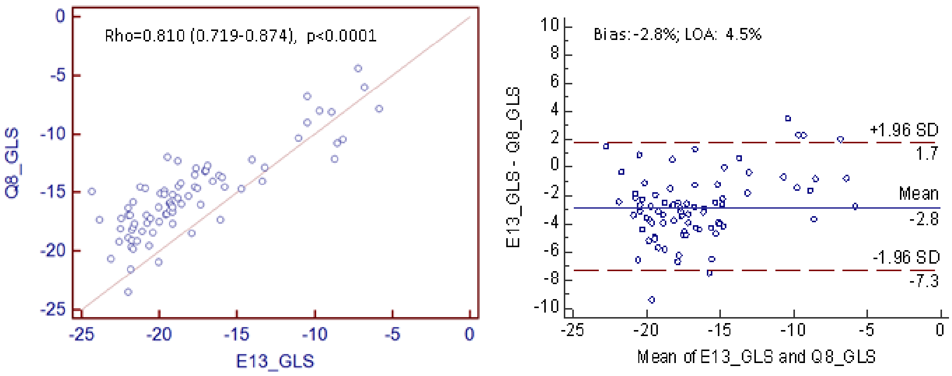
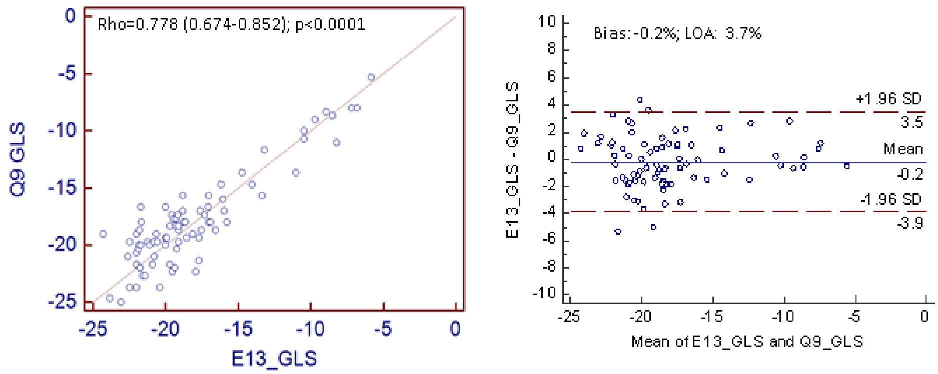


Figure appendix 4.30 -comparison between vendor

D). E13 vs Q8



E). E13 vs Q9



F). E13 vs Q10

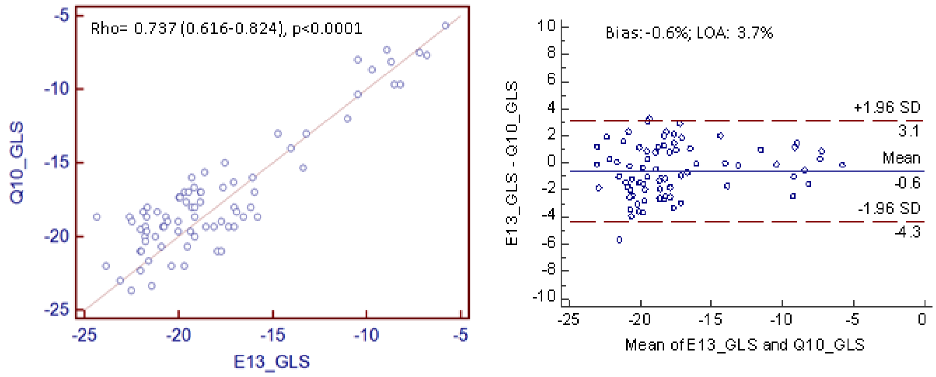
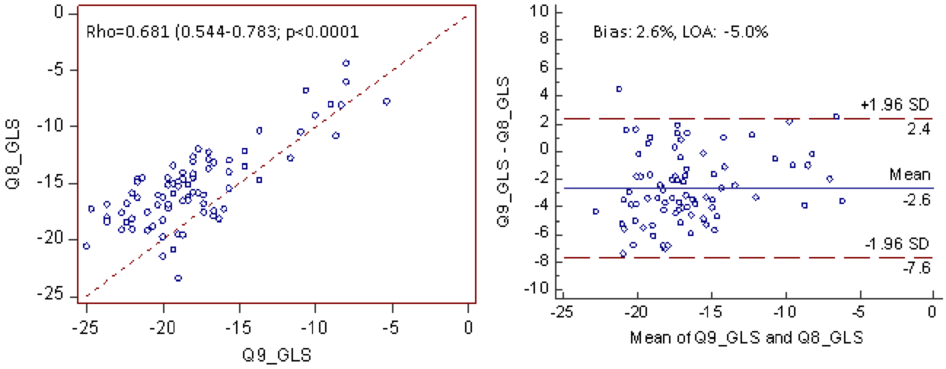
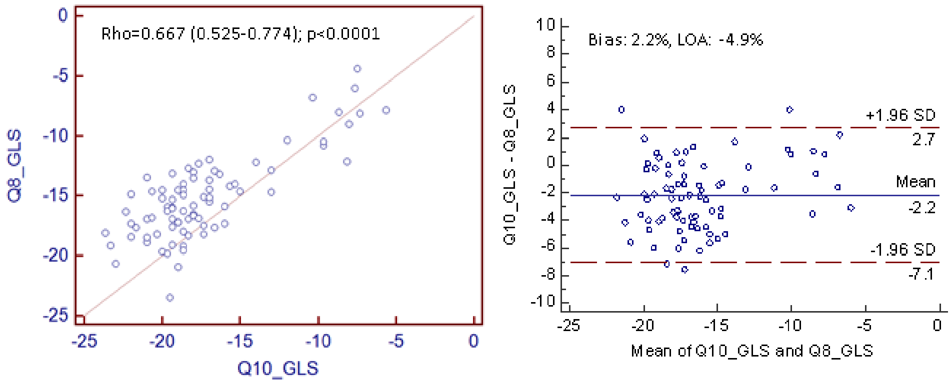


Figure appendix 4.31 -comparison within vendor

G). Q8 vs Q9



H). Q8 vs Q10



I). Q9 vs Q10

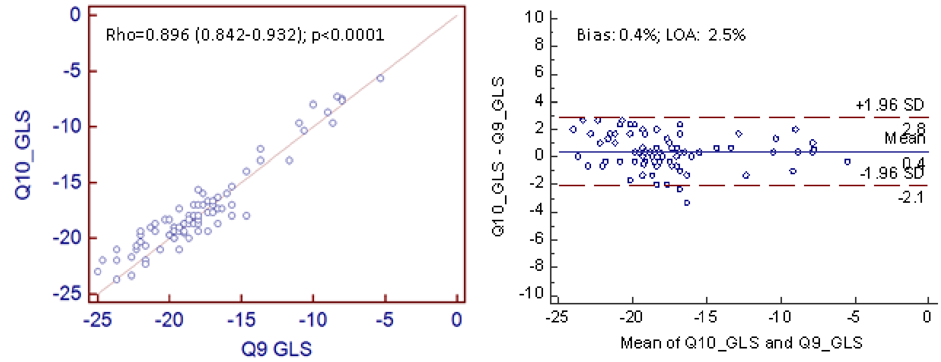


Figure appendix 4.32 -comparison within vendor

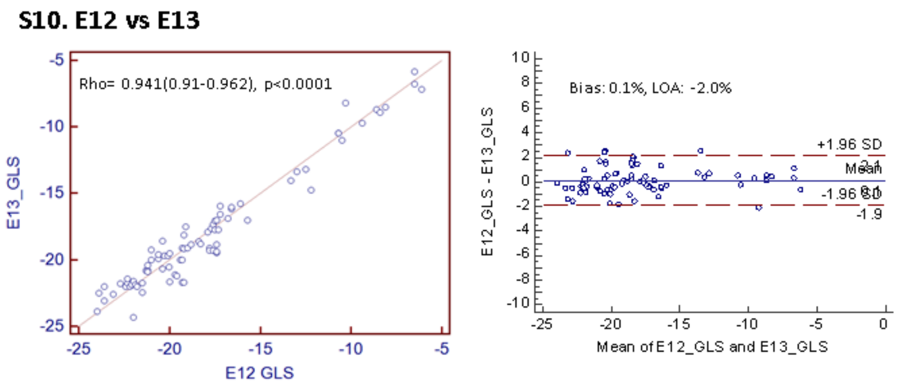


Table appendix 4.24 -Measurements of volume and strain

	Mean (SD)	Median (IQR)	Range
EDV (ml)			
GE Vivid E9	95 (41)	87 (25)	35~286
Philips iE33	102 (48)	89 (38)	48~345
ESV (ml)			
GE Vivid E9	43 (35)	33.5 (15)	12~224
Philips iE33	46 (41)	36 (18)	15~256
LVEF (%)			
GE Vivid E9	58.0 (11.8)	61 (11)	18~75
Philips iE33	58.1 (11.9)	62 (7)	14~72
GLS (%)			
Philips Q8	-15.25 (3.58)	-15.7 (4.3)	-4.4 ~ -23.5
Philips Q9	-17.91 (4.14)	-19.0 (3.3)	-5.3 ~ -25.0
Philips Q10	-17.36 (4.11)	-18.7 (3.0)	-5.7 ~ -23.7
GE E12	-17.95 (4.44)	-19.2 (4.0)	-6.1 ~ -24.0
GE E13	-18.02 (4.39)	-19.3 (4.4)	-5.8 ~ -24.3

Table appendix 4.25 -Coefficient of variance for each comparison

Variables	CV (SD)
EDV (GE/Philip) (ml)	0.10±0.07
ESV (GE/Philip) (ml)	0.13±0.09
LVEF (GE/Philip)	0.05±0.05
GLS (E12_Q8) (%)	0.12±0.08
GLS (E13_Q8) (%)	0.14±0.08
GLS (E12_Q9) (%)	0.06±0.05
GLS (E13_Q9) (%)	0.06±0.04
GLS (E12_Q10) (%)	0.07±0.04
GLS (E13_Q10) (%)	0.07±0.04
GLS (E13_E12) (%)	0.06±0.05
GLS (Q9_Q10) (%)	0.04±0.04
GLS (Q9_Q8) (%)	0.14±0.08
GLS (Q10_Q8) (%)	0.12±0.09
GLS* (E11_E12) (%)	-0.03±0.02

LVEDV (End-diastolic volume); LVESV (End-systolic volume); LVEF (Left ventricular ejection fraction); GLS (Global longitudinal strain); CV (coefficient of variation); SD (standard deviation); LOA (Limits of agreement); ICC (Intraclass correlation); E12 (EchoPAC version BT12); E13 (EchoPAC version BT13); Q10 (QLAB version 10); Q9 (QLAB version 9); Q8 (QLAB version 8)

Table appendix 4.26 -Vendor and software variability

Study	Year	(n)	Population	Acquisition	Software	Findings
Bansal et al [214]	2008	30	Ischemic heart disease	GE Vivid 7	EchoPAC 6.0 (AFI)/VVI 1.0	AFI has significantly better accuracy and 14% higher than VVI
Manovel et al [224]	2010	28	Normal subjects	GE Vivid 7 vs Toshiba Artida	EchoPAC 07/ 2D Tracking	Comparable GLS
Koopman et al[225]	2011	34	With and without cardiac disease	GE Vivid 7 vs Philips iE33	EchoPAC07/ QLAB7	Comparable GLS using VSS and VIS
Biaggi et al[226]	2011	47	Normal subjects	GE Vivid 7	EchoPAC 6.2.1/ VVI 2.0	Comparable GLS
Nelson et al[217]	2012	100	Various cardiac conditions	GE Vivid 7	TomTec 4.5/ EchoInsight 1.5.0	TomTec differs significantly from EchoInsight
Risum et al[216]	2012	30	With and without cardiac disease	GE Vivid 7 vs Philips iE33	EchoPAC 09/ TomTec 4.5	Comparable GLS using VSS and VIS
Takigiku et al[227]	2012	1000	Normal subjects	GE Vivid 7/E9 vs Philips iE33 vs Toshiba Artida	EchoPAC 11/QLAB7/Ultra-Extend	Significant difference between vendors
Negishi et al[193]	2013	45	With and without cardiac disease	GE Vivid E9 vs Philips iE33	EchoPAC 11/ QQLAB08QLAB08/ TomTec 4.5 (1.1)/EchoInsight 1.5.0	Poor Correlation with VSS, fair correlation with VIS
Sun et al[228]	2013	52	Normal subjects	GE Vivid 7 vs Philips iE33	EchoPAC 06/ QLAB 7	QLAB 7 was 10% higher than EchoPAC06
Costa et al[229]	2013	50	With and without cardiac disease	GE Vivid E9 vs Philips iE33	EchoPAC 11/ QLAB 9	AFI was 2% higher than QLAB9
Castel et al[232]	2014	64	With and without cardiac disease	GE vivid E9 vs Philips iE33	EchoPAC12/QLAB 9	Similar GLS but different in segmental strain

VIS, vendor independent software; VSS, vendor specific software

Chapter 5

Community screening in a Young population – Association of Clinical and Social Determinants with Subclinical Cardiac Function

Article "Associations of Childhood and Adult Obesity with Left Ventricular Structure and Function" was published in
International Journal of Obesity, 2017, 41(4):560-568.

Hong Yang, Kazuaki Negishi, Ying Wang, Mark Nolan, Thomas H Marwick

Chapter 5. Community Screening in Young Age

Association of Childhood and Adult obesity with Left Ventricular Structure and Function

Introduction

Heart failure is a disease of the elderly. Risk stratification and prediction are often done in the elderly. But cardiac structural and functional disturbances may happen in the young and can be detected by advanced imaging modalities. These have not been well studied in the literature. The current chapter is from a pilot sample of CDAH (childhood determinants of adult health) with 29 years' follow-up. In this cohort of healthy young adults, overweight and obesity is the only known cardiovascular risk. This chapter will discuss childhood versus adult overweight and obesity and their associations with structural and functional features of stage B heart failure by echocardiography.

The following text has been published in the ***International Journal of obesity (Lond). 2017; 41(4):560-568.***

Abstract

Background: Overweight and obesity are associated with left ventricular (LV) dysfunction. We sought whether echocardiographic evidence of abnormal adult cardiac structure and function was related to childhood or adult adiposity.

Methods: This study included 159 healthy individuals aged 7-15 years and followed until age 36-45 years. Anthropometric measurements were performed both at baseline and follow-up. Cardiac structure (indexed left atrial volume [LAVi], left ventricular mass [LVMi]) and LV function (global longitudinal strain [GLS], mitral e') were assessed using standard echocardiography at follow up. Conventional cut-offs were used to define abnormal LAVi, LVMi, GLS and mitral annular e'.

Results: Childhood body mass index (BMI) was correlated with LVMi ($r=0.25$, $p=0.002$), and child waist circumference was correlated with LVMi ($r=0.18$, $p=0.03$) and LAVi ($r=0.20$, $p=0.01$), but neither were correlated with GLS. One standard deviation (by age and sex) increase in childhood BMI was associated with LV hypertrophy (RR: 2.04 [95% CI: 1.09, 3.78]) and LA enlargement (RR: 1.81 [95% CI: 1.02, 3.21]) independent of adult BMI, but the association was not observed with impaired GLS or mitral e'. Cardiac functional measures were more impaired in those who had normal BMI as child but had high BMI in adulthood ($p<0.03$), and not different in those who were overweight or obese as a child and remained so in adulthood ($p>0.33$).

Conclusions: Childhood adiposity is independently associated with structural cardiac disturbances (LVMi and LAVi). However, functional alterations (GLS and mitral e') were more frequently associated with adult overweight or obesity, independent of childhood adiposity.

5.1 Background

The obesity epidemic is a relatively recent health problem, with more than doubling of the prevalence of obesity from 1962 to 2000 in the United States and worldwide[233,234]. More than one in three adults in the United States and more than one in four in Australia are obese[235]. The prevalence among children and adolescents has also increased and continues to do so[235,236]. In addition to its impact on childhood health, a major concern about childhood obesity is that it may adversely affect health in adulthood[237]. The longitudinal progression of adiposity and associated adult risk of cardiovascular disease (CVD) has been established in large population studies[238-241], which have mainly focused on cardiovascular risk factors and morphologic changes including carotid intima-media thickness (IMT) and left ventricular (LV) mass index (LVMi). However, the independent relationship between childhood obesity and adult CVD risk is controversial. The risk of CVD among overweight or obese children who became non-obese by adulthood is similar to those who were never obese[242], while those who were normal or at the lower end of the weight scale in childhood and became obese as an adult have the worst CVD outcome[243]. Thus, while there is clearly a need to control childhood obesity, the development of obesity over the life course also needs attention. Indeed, our previous results suggested that large artery stiffness appeared to be dependent primarily on current adiposity and magnitude of adiposity gain from childhood[244]. The importance of the development of obesity is demonstrated in another of our previous studies to assess LVMi[245].

In addition to changes in morphology, obesity may cause functional disturbances, independent of structural changes[246,247], and to which conventional echocardiographic measures (eg. left ventricular ejection fraction, LVEF) are insensitive[82]. Myocardial strain is a sensitive and robust echocardiographic marker of myocardial deformation that has been used to detect subtle myocardial impairment in patients with hypertension[248], diabetes[97], obesity and metabolic syndrome[73] in the presence of normal LVEF. As asymptomatic LV dysfunction is associated with progression to heart failure (HF), the independent risk of childhood adiposity for cardiac functional alterations is a key research question.

5.2 Aims and Hypothesis

In the light of our previous work on obesity and LV dysfunction,[249] we hypothesized that current obesity is the main problem linked with cardiac *functional* changes. If this were the case, early myocardial dysfunction would be likely to be associated more with adult adiposity and less by childhood adiposity. We sought to investigate whether childhood adiposity was associated with adult subclinical myocardial dysfunction.

5.3 Methods

Study population. This work was performed in a follow-up substudy of subjects enrolled in the Childhood Determinants of Adult Health (CDAH) study, a prospective, nationwide cohort of Australian children aged 7-15 years (n=8498), who participated in the 1985 Australian Schools Health and Fitness Survey (ASHFS).[250] The sampling method has been described elsewhere.[251] We completed comprehensive echocardiographic assessments in a subset of 159 adult participants who first participated in the ASHFS in 1985, by selecting subjects at two sites for detailed myocardial function analysis. The study was approved by the Tasmanian Human Ethics Committee, and all individuals gave written informed consent.

Body size or adiposity. Weight, height, waist and hip circumference were measured in childhood and adulthood.[252] Body mass index (BMI) was calculated as weight (kg)/height (m) ^{2}. Body surface area was measured as [weight (kg) x height (cm)/3000]$^{0.5}$. Waist circumference (WC) in childhood was measured at the level of the umbilicus to the nearest 0.1 cm. WC in adulthood was measured at the narrowest point between the lower costal border and the iliac crest to the nearest 0.5 cm. Waist-to-hip and waist-to-height ratios were calculated as waist (cm)/hip (cm) and waist (cm)/height (cm) respectively. Childhood body habitus was classified as healthy weight, overweight or obese using IOTF (International Task Force) age- and gender-specific cut-offs.[253] Adult adiposity was classified as normal weight (BMI$<$25 kg/m^2), overweight (25$\leq$BMI$<$30 kg/m^2) and obese (BMI$\geq$30 kg/m^2). Blood pressure was measured from the right brachial artery three times using a digital automatic blood pressure monitor (Omron HEM907, Omron Healthcare Inc, Japan), after participants had been sitting for at least 5 minutes. The mean of the three measurements was used. High blood pressure was defined as systolic blood pressure (SBP)/diastolic blood pressure (DBP) $>$140/90 mmHg.

Echocardiographic study. Standard transthoracic 2D and Doppler echocardiographic studies were performed using standard equipment (Siemens SC2000, Siemens Healthcare, Mountain View, CA) and transducers (4V1c, 1.25-4.5 MHz; 4Z1c, 1.5-3.5 MHz) in accordance with the American Society of Echocardiography (ASE) guidelines[187,188]. Left ventricular (LV) dimensions during diastole and systole and wall thicknesses were measured according to the recommended criteria. [187] LV mass was indexed to body height using LVM/height$^{1.7}$[254]. LV hypertrophy (LVH) was defined as LVM index $>$75 g/m$^{1.7}$ in men and $>$57 g/m$^{1.7}$ in women[254]. LV and left atrial (LA) volumes were calculated by the Simpson biplane method[187], and LA volume was indexed to body surface area, with LA enlargement (LAE) defined as LAVi$\geq$34 ml/m^2[187]. Mitral inflow peak early diastolic velocity (E), peak late diastolic velocity (A), E/A ratio, E wave deceleration time (DecT) were measured for diastolic function assessment[188]. Tissue Doppler mitral annular early diastolic velocity (e') was assessed at septal and lateral, averaged e' $<$10 was used as cut-off[188]. Averaged E/e'$>$14 was defined as cutoff for abnormal[188]. LV peak longitudinal strain measurements were obtained from grey scale-recorded images in the apical 4-chamber, 2-chamber and long-axis views. Strain was analysed using velocity vector imaging (Syngo VVI, Siemens Medical Solutions). GLS was measured by averaging strain from the regional of interest in the apical 4-chamber, 2-chamber and long-axis views. Impaired GLS was defined using cut-off of <18 %[85].

Biomarkers. A 30 ml blood sample was taken from the antecubital vein after at least 8 hours of fasting. Fasting glucose, triglycerides, high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol were analysed. C-reactive protein (CRP) level was also obtained. Biomarkers were collected only in a subgroup of children at baseline.

Statistical analysis. Child BMI was converted to z-score specific to each sex and year of age by subtracting from each measurement the mean for that sex and age category and dividing by its standard deviation (SD). Data are presented as mean ±SD after testing for normal distribution (Shapiro-Wilk test). Data deviating from normality are expressed as median (inter-quartile range [IQR]). Categorical variables are expressed as percentages. For differences among groups, the Mann-Whitney U test was used for continuous variables and X^2 tests or Fisher's exact test for categorical variables. Associations between variables were assessed with Pearson or Spearman correlation coefficients. Multi-group comparison was performed by the analysis of variance with Bonferroni post hoc analysis when data showed a normal distribution. Otherwise, the Kruskal-Wallis test was used for comparison of non-normally distributed variables. Linear regression analysis was used to examine the associations between body size or adiposity and echo variables. Logistic regression was used to examine the association of adult adiposity with abnormal cardiac measures using conventional cut-offs. Statistical analyses were performed using a standard statistical software package (SPSS software 22.0, SPSS Inc., Chicago, IL). Statistical significance was defined by $p< 0.05$.

5.4 Results

Baseline characteristics. The mean follow-up time among the total 159 participants (age 40.2±2.8, range 36-45 years, 47% male) was 28.9±0.1 years. Table 5.27 summarizes the participants' characteristics at baseline and at follow-up. Men generally had higher BMI at baseline and follow-up.

Progression of overweight and obesity. According to IOTF age- and gender-based cut-offs at baseline, 18 (11.3%) children were classified as ≥overweight and 2 (1.3%) was obese. During follow-up, 93 (59%) adults were categorized as ≥ overweight and 29 (18%) were obese. 55% (78/141) of children of normal weight had progressed to either overweight (38%, 53/141), or obese (18%, 25/141) while 94% (15/16) of overweight children remained overweight (11/16) or obese (4/16) into adulthood. Of the 2 obese child at baseline, one became normal weight and one became overweight (Figure appendix 5.36)**.**

Table 5.27 Participant characteristics at baseline and follow-up

	Female (n=85)	Male (n=74)
Child		
Age, mean ±SD)	10.2±2.8	11.4±2.5
Age Range	7-15	7-15
Height (cm)	140.3±14.9	149.4±15.2
Weight (kg)	35.5±11.3	41.8±12.3
Body Mass Index (g/m2)	17.5±2.5	18.3±2.3
Waist (cm)	59.1±7.2	64.6±7.1
Hip (cm)	73.7±9.6	77.2±9.7
Waist-Height ratio	0.42±0.04	0.43±0.03
Waist-Hip ratio	0.80±0.05	0.84±0.04
Overweight Obese, n (%)	10 (12)	8 (11)
Adult		
Age, mean ±SD	39.7±2.9	40.9±2.5
Age Range	36-45	36-45
Height (cm)	165.5±6.4	179.0±6.9
Weight (kg)	69.1±14.7	86.1±13.1
Body Mass Index (g/m2)	25.2±4.9	26.8±3.7
Waist (cm)	76.8±11.3	89.9±10.4
Hip (cm)	101.1±10.9	102.7±6.4
Waist-Height ratio	0.46±0.07	0.50±0.06
Waist-Hip ratio	0.76±0.05	0.87±0.07
Overweight, n (%)	41 (48)	52 (70)
Obese, n (%)	15 (18)	14 (19)
Systolic blood pressure	108 (9)	123 (13)
Diastolic blood pressure	68 (7)	74 (10)
Blood Glucose (mmol/L)	4.6 (4.3-4.8)	4.8 (4.5-5.1)
Creatinine (mmol/L)	58 (53-63)	77 (69-85)
C-reactive protein (mg/L)	0.56 (0.16-2.13)	0.63 (0.22-2.97)
Insulin (mIU/L)	3.0 (2.0-5.0)	5.0 (3.0-7.8)
Total Cholesterol (mmol/L)	4.8 (4.2-5.4)	5.1 (4.5-5.7)
Adult Echo characteristics		
Structural measures		
Relative wall thickness	0.38±0.05	0.39±0.04
Left ventricular volume (ml/m2)	51±9	56±9
Left ventricular mass index (Ht^1.7) (g/m2)	53±11	60±11
Left atrial volume index (ml/m2)	27.9±6.4	28.4±6.0
Functional measures		
Left ventricular ejection fraction (%)	61 (5)	58±5
Global longitudinal strain (%)	21±2	19±2
Mitral inflow E/A	1.8±0.6	1.6±0.4
Mitral Deceleration time (ms)	207±49	208±52
Mitral annular early diastolic velocity e' (cm/s)	13.4±2.1	12.5±2.0
Mitral early diastolic flow/annular velocity E/e'	6.1±1.3	5.6±1.4

Echocardiographic characteristics. Cardiac structure and function at follow-up are summarized in Table 5.27. Using conventional cut-offs, the prevalence of LA enlargement (LAE), LV hypertrophy (LVH), impaired GLS and abnormal e' were 16%, 19%, 16%, 6.3% respectively. None had abnormal E/e' by conventional cut-off. The detailed correlations of various body size metrics (including height, weight, BMI, WC, Hip, Waist-height ratio, Waist-hip ratio) as child and as adult with adult cardiac structural (including LAVi, LVMi) and functional (including mitral e', E/e' and GLS) measures are summarized in Table appendix 5.31.

Childhood body BMI was correlated with LVMi (r=0.25, p=0.002), and child WC was correlated with LVMi (r=0.18, p=0.03) and LAVi (r=0.20, p=0.01), but neither were correlated with mitral e' and E/e', nor with GLS. Of all adult body size metrics, BMI and WC showed stronger association with both structural and functional measures including LVMi, mitral e', E/e' and GLS (Table appendix 5.32). Figure 5.33 shows the correlation of GLS with adult BMI and WC, not with childhood BMI, nor with child WC. The relationship of GLS with childhood WC and BMI demonstrated a non-linear pattern. In addition, the association of adult WC with GLS seemed to be stronger (r=-0.362, p<0.001) than that of BMI (r=-0.164, p=0.39) (Figure 5.33).

Association of change in body habitus with cardiac structure and function. Table 5.28 shows the estimated response of adult cardiac changes to one standard deviation (SD) increase in childhood BMI and WC before and after adjustment of adult BMI and WC. Of the structural measures, increase in child BMI was associated with age and gender–specific increase of LVMi, independent of adult systolic blood pressure and other cardiovascular risk factors including glucose, insulin and blood lipids. However, these associations substantially attenuated after adjustment for adult BMI. In contrast, adult BMI and WC remained significant associations with or without the presence of childhood weight metrics. Of the functional measures, adult BMI and WC were significantly associated with adverse diastolic functional measure (e') independent of child BMI and WC. Adult BMI and WC were not associated with systolic functional measure (GLS). Childhood WC demonstrated a positive association with e' and GLS. However, in the presence of adult BMI and WC, these positive associations became more prominent and statistically significant, suggesting the increased body weight gain from childhood was positively associated with systolic and diastolic functional measures (Table 5.29).

One standard deviation (SD) (by age and gender) increase in childhood BMI (2.4 g/m^2) was associated with greater risk of adult LAE (RR: 1.81 [95% CI: 1.02, 3.21]) and LVH (RR: 2.04 [95% CI: 1.09, 3.78]), one SD (by age and gender) increase of child WC (7.6 cm) was associated with greater risk of LAE (RR: 2.05 [1.26, 3.34]) independent of adult BMI and WC (Table appendix 5.33).

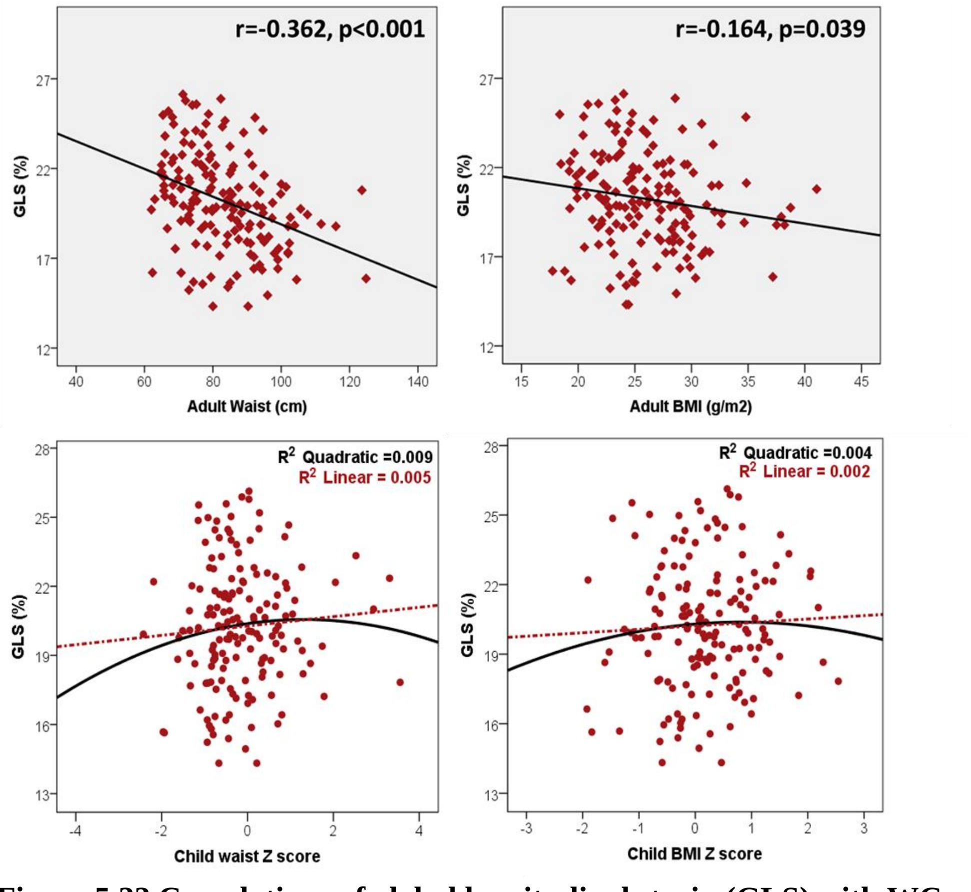


Figure 5.33 Correlations of global longitudinal strain (GLS) with WC and BMI

Figure shows: 1) adult adiposity is strongly associated with GLS, more than child adiposity. 2) Child weight showed narrow distribution and very few above Z score 2, therefore, a positive association if using linear model. 3) Quadratic model yields a higher r^2 showed a trend of negative relationship beyond Z score of 2.

Table 5.28 Correlation of child and adult body adiposity with structural and functional cardiac measurements.

	LAVi		LVMi		E/e'		e'		E/A		GLS	
	r	p value	r	p value	r	p value	r	p value	r	p value	r	p value
Child												
Age	-0.045	0.576	0.095	0.232	0.024	0.771	-0.231	0.004	-0.243	0.002	-0.039	0.626
Height (cm)	0.021	0.794	0.134	0.092	0.045	0.582	-0.242	0.002	-0.268	0.001	-0.035	0.665
Weight (kg)	0.046	0.568	0.18	0.023	0.091	0.258	-0.197	0.013	-0.234	0.003	0.004	0.961
Body Mass Index (g/m2)	0.147	0.066	0.246	0.002	0.098	0.223	0.025	0.755	0.049	0.544	0.046	0.562
Waist circumference (cm)	0.198	0.012	0.177	0.026	0.039	0.630	0.149	0.062	0.112	0.164	0.071	0.374
Hip (cm)	0.057	0.481	0.174	0.026	0.087	0.283	-0.124	0.122	-0.169	0.036	0.040	0.622
Waist-Height ratio	0.130	0.104	0.180	0.024	-0.020	0.809	0.207	0.009	0.127	0.115	-0.014	0.862
Waist-Hip ratio	0.057	0.481	0.140	0.080	-0.133	0.099	0.107	0.184	0.034	0.679	-0.154	0.054
Adult												
Height (cm)	0.140	0.079	0.224	0.004	-0.136	0.090	-0.153	0.055	-0.127	0.114	-0.324	<0.001
Weight (kg)	0.026	0.744	0.381	<0.001	0.085	0.294	-0.305	<0.001	-0.275	0.001	-0.313	<0.001
Body Mass Index (g/m2)	-0.055	0.489	0.342	<0.001	0.194	0.016	-0.289	<0.001	-0.257	0.001	-0.164	0.039
Waist circumference (cm)	-0.071	0.489	0.394	<0.001	0.085	0.293	-0.350	<0.001	-0.336	<0.001	-0.362	<0.001
Hip (cm)	-0.019	0.813	0.293	<0.001	0.176	0.029	-0.222	0.005	-0.165	0.041	-0.083	0.298
Waist-Height ratio	-0.135	0.094	0.350	<0.001	0.151	0.062	-0.323	<0.001	-0.316	<0.001	-0.267	0.001
Waist-Hip ratio	-0.076	0.343	0.334	<0.001	-0.016	0.842	-0.345	<0.001	-0.361	<0.001	-0.474	<0.001

r: correlation coefficient; LAVi: left atrial volume index; LVMi left ventricular mass index; e’: mitral annular early diastolic tissue velocity;
E/e’: mitral inflow peak early diastolic velocity/mitral annular early diastolic tissue velocity; GLS: global longitudinal strain

Table 5.29 Association of adult cardiac structural and function in childhood and in adulthood.

	LAVi			LVMi			e'			GLS		
	R^2	β (95% CI)	p	R^2	β (95% CI)	p	R^2	β (95% CI)	p	R^2	β (95% CI)	p
Body Mass Index (BMI)												
Child BMI only	0.024	0.14 (-0.11, 2.26)	0.08	0.132	0.20 (0.06, 0.41)	0.01	0.082	0.06 (-0.11, 0.25)	0.46	0.258	0.14 (-0.03, 0.33)	0.05
Child BMI adjusted for adult BMI	0.037	0.19 (0.02, 0.43)	0.03	0.191	0.11 (-0.06, 0.31)	0.19	0.162	0.17 (0.01, 0.39)	0.04	0.281	0.19 (0.06, 0.41)	0.01
Adult BMI only	0.007	-0.06 (-0.22, 0.10)	0.47	0.181	0.30 (0.16, 0.45)	<0.01	0.138	-0.25 (-0.39, -0.09)	0.01	0.248	-0.09 (-0.24, 0.05)	0.18
Adult BMI adjusted for child BMI	0.037	-0.13 (-0.29, 0.04)	0.14	0.191	0.26 (0.11, 0.42)	0.01	0.162	-0.31 (-0.47, -0.15)	<0.01	0.281	-0.17 (-0.31, -0.02)	0.03
Waist Circumference (WC)												
Child WC only	0.040	0.19 (0.04, 0.19)	0.02	0.127	0.26 (0.05, 0.47)	0.02	0.101	0.15 (-0.001, 0.32)	0.05	0.254	0.17 (-0.02, 0.37)	0.08
Child WC adjusted for adult WC	0.063	0.23 (0.08, 0.42)	0.01	0.179	0.14 (-0.08, 0.36)	0.22	0.206	0.24 (0.09, 0.41)	0.002	0.293	0.28 (0.07, 0.48)	0.01
Adult WC only	0.013	-0.11 (-0.29, 0.07)	0.23	0.170	0.32 (0.15, 0.49)	<0.01	0.138	-0.25 (-0.39, -0.09)	0.001	0.260	-0.17 (-0.33, -0.01)	0.04
Adult WC adjusted for child WC	0.063	-0.18 (-0.37, 0.01)	0.05	0.170	0.28 (0.10, 0.46)	0.002	0.206	-0.38 (-0.56, -0.21)	<0.01	0.293	-0.24 (-0.41, -0.08)	0.01

Each model contains age and gender.
BMI: body mass index; LAVi: left atrial volume index; LVMi left ventricular mass index; E/e': mitral early diastolic peak velocity/mitral early diastolic tissue velocity; GLS: global longitudinal strain

Table 5.30 Echocardiographic and biomarkers in participants cross-classified by child and adult BMI status.

	Child-/Adult- (n=63)	Child-/Adult+ (n=78)	Child+/Adult+ (n=15)	p	P (1-2)	P (1-3)	P (2-3)
Blood Pressure							
SBP	111±11	119±14	116±14	<0.01	<0.01	0.12	0.42
DBP	67±7	74±10	70±9	<0.01	<0.01	0.22	0.11
Adult HTN, n (%)	1 (1.6)	9 (12)	1 (7)	0.07	0.02	0.35	0.58
Adult Echo characteristics							
Left ventricular mass (Ht^1.7) (g/m2)	52±10)	59 (10)	61±13	<0.01	<0.01	0.01	0.57
Left atrial volume index (ml/m2)	28±7	28±5	28±6	0.86			
Global longitudinal strain (%)	21±3	19±3	21±2	0.14			
Mitral inflow E/A	1.9±0.5	1.6±0.4	1.8±0.5)	<0.01	<0.01	0.78	0.03
e' (cm/s)	13.6±2.2	12.3 (1.9)	13.0 (1.9)	<0.01	<0.01	0.36	0.23
E/e'	5.6±1.3	6.1±1.3	6.0±1.1	0.04	**0.03**	**0.33**	0.71
Adult Echo characteristics, categorical							
LV hypertrophy, n (%)	4 (6)	19 (24)	6 (40)	0.02	0.01	<0.01	0.21
Enlarged left atrium	9 (14)	12 (15)	3 (20)	0.86			
Impaired GLS, n (%)	9 (14)	15 (19)	1 (7)	0.43			
Reduced e' (cut-off 10)	3 (5)	7 (9)	0 (0)	0.34			
Biomarkers							
Blood Glucose (mmol/L)	4.5 (4.2-4.8)	4.8 (4.6-5.1)	4.6 (4.4-4.7)	<0.01	<0.01	0.40	0.22
Creatinine (mmol/L)	63 (56-73)	68 (56-81)	66 (58-70)	0.38			
C-reactive protein (mg/L)	0.2 (0.1-0.6)	1.6 (0.4-4.1)	1.0 (0.3-2.1)	<0.01	<0.01	0.03	0.13
Insulin (mIU/L)	3 (2-4)	5 (4-8)	4 (2-6)	<0.01	0.01	0.29	0.35
Total Cholesterol (mmol/L)	4.9 (4.3-5.4)	5.1 (4.3-5.7)	4.8 (4.4-6.2)	0.45			
Triglycerides (mmol/L)	0.7 (0.6-0.9)	1.1 (0.8-1.6)	0.8 (0.6-1.1)	<0.01	<0.01	0.31	0.13
HDL (mmol/L)	1.6 (1.4-1.9)	1.3 (1.0-1.5)	1.6 (1.2-1.7)	<0.01	<0.01	0.23	0.07
LDL (mmol/L)	2.9 (2.3-3.3)	3.1 (2.5-3.9)	3.0 (2.2-3.7)	0.09	0.03	0.29	0.73

Child-/adult: normal child/normal adult weight; child-/Adult+: normal child but overweight or obese adult; Child+/Adult+: overweight child/overweight or obese adult

Participants were then divided into three groups according to results of progression of BMI status from childhood and adulthood; normal child and adult BMI (Child-/Adult-, n=63); normal child but high adult BMI (Child-/Adult+, n=78) and high child and adult BMI (Child+/Adult+, n=15). Only 3 participants had abnormal child but normal adult BMI and were not included for further study. Table 5.29 presents the clinical, cardiac and biomarker findings of the three groups. Child-/Adult+ had significantly higher blood pressure and more adult hypertension, relatively more impaired cardiac functional measures including mitral e’, higher E/e’ and more LVH. Child+/Adult+ group had similar functional measures compared to Child-/Adult- but more impaired structural changes. Results of biomarkers were similar between Child-/Adult- and Child+/Adult+, but more abnormal in Child-/Adult+.

To further demonstrate the magnitude of weight gain on cardiac changes, we further separated Child-/Adult+ into two subgroups based on overweight (Child-/Adult overweight) and obese (Child-/Adult obese) and compared cardiac changes with controls (Child-/Adult-) and with (Child+/Adult+). Figure 5.34 emphasizes the role of adult overweight and obesity as a driver of LVH and diastolic dysfunction, rather than systolic impairment. These findings parallel the presence of metabolic disturbance and inflammation in overweight and obese adults (Figure 5.35).

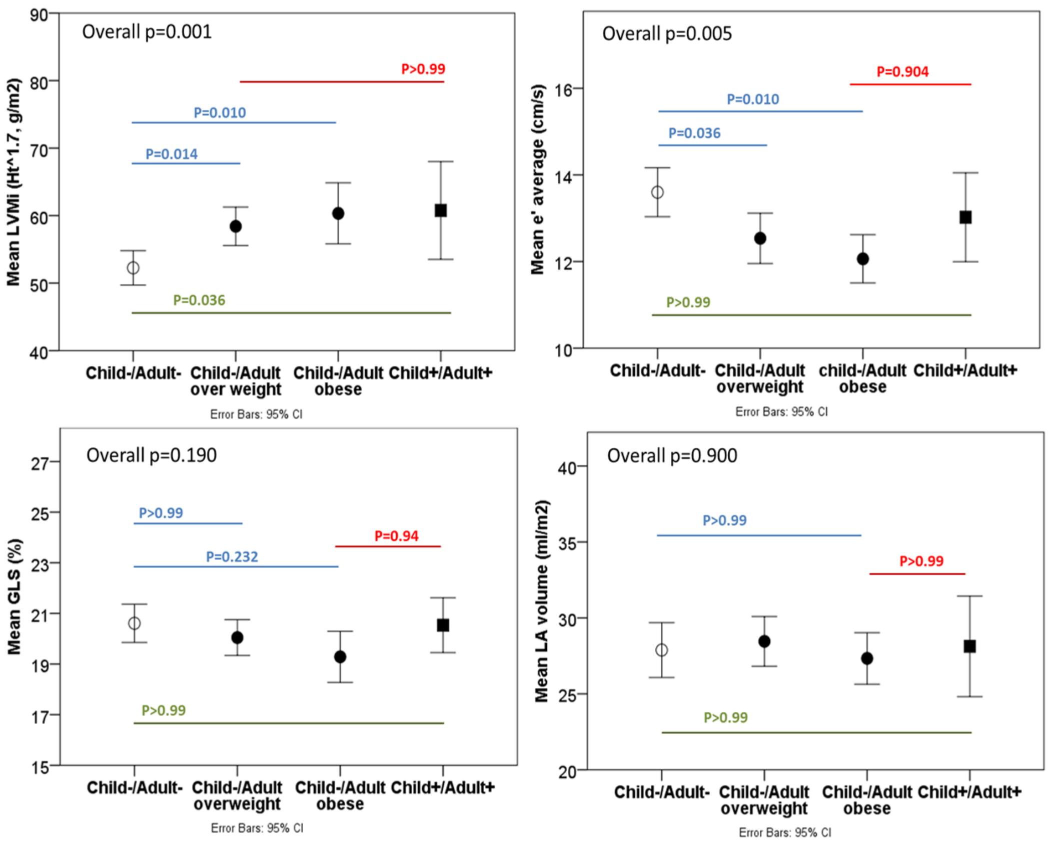


Figure 5.34 Cardiac structure and function cross-classified by child and adult BMI

Among adults of overweight/obesity, no differences were detected in their cardiac structure and function between who were normal in childhood versus who were overweight/obese in childhood (labels in red). Among those who were normal in childhood, those who became overweight/obese in adulthood had structural and function cardiac abnormalities (labels in blue). Abnormal structural (normal functional) change was detected in those who were abnormal in childhood as compared to who were normal (labels in green).

Group 1 (open circle, n=63, normal adult, normal child BMI);
Group 2 (close circle, n=53, overweight adult, normal child BMI);
Group 3 (close circle, n=25, obese adult, normal child BMI);
Group 4 (square, n=15, overweight/obese adult, overweight/obese child BMI).

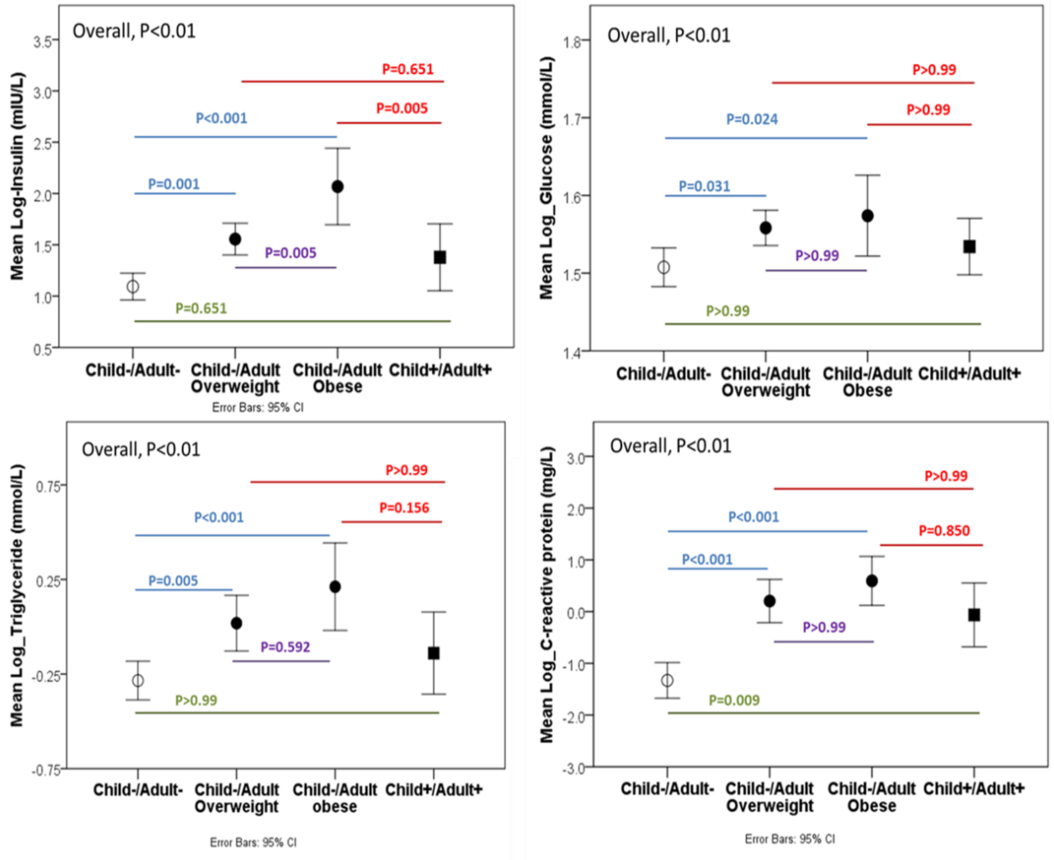


Figure 5.35 Biomarkers in participants cross-classified by child and adult BMI
Comparing group 4 versus 3&2 (red), no differences were observed except for insulin level, indicating most biomarker were elevated in overweight/obese adult regardless of their childhood obesity history. Comparing group 1 versus the rest (blue), indicating the development of overweight/obese is associated with significantly increased biomarkers. Comparing group 1 versus 4 (green), CRP was significantly higher in group 4 indicating the presence of inflammatory status although no difference was detected in their insulin, glucose and triglyceride levels. Comparing group 2 and 3 (purple), no difference was observed between adult overweight versus obese except for obese individual had higher insulin levels.
Group 1 (open circle, n=63, normal adult, normal child BMI);
Group 2 (close circle, n=53, overweight adult, normal child BMI);
Group 3 (close circle, n=25, obese adult, normal child BMI);
Group 4 (square, n=15, overweight/obese adult, overweight/obese child BMI).

5.5 Discussion

In this longitudinal study over almost 30 years, we assessed the association of current and past adiposity with adult cardiac structure and function. The findings showed: 1) adult overweight and obesity were associated with adverse cardiac function independent of childhood weight status, 2) childhood adiposity was associated with adult structural cardiac disturbances independent of adult adiposity, 3) disturbances of cardiac function were most pronounced in those who had increased adiposity in adulthood, and seem to parallel the severity of their metabolic disturbance.

Association of LV structure and function with obesity. Obesity is linked with alterations of LV structure and function in adults[255] and children.[256,257] Functional alterations often precede and accompany structural changes, and may lead to the clinical syndrome of obesity cardiomyopathy.

Studies investigating obesity-related cardiac dysfunction has shown a number of features. First, abnormalities of cardiac structure and function do not require morbid obesity (BMI >35). Application of new imaging markers including tissue velocity (e' and E/e') and speckle tracking echocardiography (GLS) have shown myocardial alterations in overweight (BMI, 25 to 30) and mildly obese (BMI, 30 to 35) individuals,[255,258] perhaps because these markers are more sensitive to subtle myocardial damages than are conventional markers[259]. The assessment of subtle cardiac dysfunction using tissue Doppler and speckle tracking has mostly been performed in cross sectional studies. In contrast, this study uses a longitudinal population sample to address the importance of functional alterations because early cardiac dysfunction is a precursor stage of overt heart failure and may lead to adverse outcome. The longitudinal sample allowed us to assess adiposity change from childhood and the magnitude of adiposity gain to be important predictors. Our results are in agreement to other studies using tissue Doppler imaging that showed depressed diastolic function in obese young adults[255,260]. In addition, we showed a positive association of child BMI and WC with e' and GLS in the presence of increased adult BMI and WC. This suggests that increased gain of adipose tissue is associated with both systolic (GLS) and diastolic (tissue Doppler e') alterations. Second, the effects of obesity on the heart varies from asymptomatic LV dysfunction to overt dilated cardiomyopathy. These abnormal findings can be found in individuals who are otherwise young (<40 year) and healthy[260] and with no evidence of hypertension, diabetes, metabolic disturbance and inducible coronary artery disease by stress testing.[255] In the current study cohort of young (≤ 45 year) and healthy individuals with no known history of diabetes, hypertension and coronary artery disease, the prevalence of structural abnormalities using guideline-recommended cut-offs[187] was 16% by LAE, 19% by LVH, 16% by impaired GLS and 6.3% by impaired e'. These observations support the notion that depressed LV function is already present in relatively young, overweight/obese people even if clinical features of common comorbidities and other associated disease are not evident. Third, the effect of weight loss on cardiac functional improvement has been variable, which implies that cardiac impairment may not be completely reversible. Many factors contribute to outcomes, mostly the magnitude and duration of obesity as well as the magnitude and duration of cardiac damage, and both may worsen with the development of codominant comorbidities.[261,262]

The potential implications of change of obesity with time. Obese children are at risk of being obese as adults[263,264] which leads to an increased risk of cardiac structural and functional impairment. The prognostic implications of childhood obesity has been studied in large population studies.[242] Although most evidence has been based on obesity-related metabolic disturbance,[240] the impact of childhood obesity in the development of adult left ventricular hypertrophy has been demonstrated[265,266]. However, no studies have assessed the impact of childhood obesity on adult cardiac function. In our study, there was not enough evidence to demonstrate the independent association of childhood body size. We suspect a few possible contributing factors: 1) a relatively "healthy childhood population" with only 11.3% overweight and 1.3% obese children; 2) a possible non-linear relationship between childhood BMI and functional measures; 3) adult cardiac functional changes are more associated with adult body adiposity and characteristics. Cardiac functional impairment in adulthood is an indication of adverse outcome and disease progression.

Whether childhood obesity is an independent predictor of adverse adult outcome has been challenged in the recent literature. In a systematic review by Lloyd, evidence indicated that children with low BMI but overweight in adulthood[243] had the highest risk of CVD. In another systematic review and meta-analysis, Llewellyn and Simmonds challenged the conventional view of using childhood BMI predicting adult morbidity.[267] [264] The authors concluded that childhood obesity is associated with moderately increased risk of adult morbidity but that the association was not strong enough to predict outcome. This was due to the fact that most weight-related morbidities occurred in individuals who were of healthy weight as a child. In our study, after adjustment for adult body size, the magnitude of adiposity change seemed to be associated with alteration of both GLS and e'. It likely that the duration of obesity is an important determinant of cardiac function changes and subsequent adverse outcomes, but we were unable to gather this information in our study[268]. Further research is needed to explore the effects of the time course of weight change.

The mechanism of cardiac dysfunction and metabolic disturbance. The progression of cardiac dysfunction in obese individuals is influenced by a variety of determinants including genetic and environmental influences.[269] In adulthood, obesity often coexists with weight-related comorbidities, mostly diabetes and hypertension, which further complicates the cardiac manifestations. First, cardiac preload is increased in obese individuals due to increased metabolic demand[270,271]. In the absence of myocardial dysfunction, this may explain the observation of increased or supernormal LV ejection fraction.[249] Second, cardiac afterload is also increased due to alterations of arterial resistance and stiffness.[249] Obesity related insulin resistance plays an important role by causing arterial wall smooth muscle cell damage (which alters stiffness and resistance), and myocardial cell apoptosis and cardiac dysfunction.[272] Third, a combination of inflammatory, metabolic and neurohormonal changes lead to myocardial fibrosis, causing both cardiac systolic and diastolic dysfunction.[73] The presence of metabolic disturbance in this cohort is demonstrated by the subgroup of child-/adult+, who had the highest insulin, glucose and triglyceride levels (Figure 5.35). C-reactive protein was significantly higher in all three groups with increased adult weight as compared with normal adult weight, reflecting the inflammatory process associated with obesity. Functional measures in child+/adult+ were relatively preserved and similar to those of child-/adult- (Figure 5.34), suggestive of functional cardiac changes are associated with adiposity gain. Interestingly, this subgroup had lower levels of metabolic and inflammatory markers than other obese and overweight patients (Figure 5.35), indicating that adiposity gain may be the key determinant.

5.6 Study Limitation

This study has several limitations. First, it comprises a small study population, obtained from two sites (Tasmania and Victoria), which we thought likely to be representative of the rest. The influence of progression of body weight at populational level, i.e. social economical and environmental factors cannot be excluded. Echocardiographic assessment of cardiac function needs to be further explored in the full cohort in all sites. Second, at baseline in 1985, this study cohort was relatively healthy, only 11% classified as overweight and 0.6% obese. This has limited our ability to track changes of cardiac function in relation to their weight status. Third, echocardiography was not performed at baseline. Fourth, the duration of obesity and adiposity gain was not available. Fifth, baseline blood pressure and biochemistry was not adjusted as potential confounders due to the limited data points available at follow-up. These are potential independent risk factors affecting adult cardiac function, and the potential impact needs to be further explored.

5.7 Conclusion

Childhood adiposity is independently associated with structural cardiac disturbance (LVMi and LAVi). However, cardiac functional alterations (abnormal GLS and mitral e') were more frequently associated with adult overweight/obese independent of childhood adiposity.

Postscript

Findings from this study suggested future studies needs to focus on the following: 1) Tracking changes from overweight/obese children with cardiac dysfunction into adulthood and association with outcome. 2) Understanding the duration and magnitude of adiposity gain and the duration of cardiac dysfunction and association with cardiac dysfunction.

Next chapter is a cross-sectional analysis to examine and understand the two most commonly prevalent non-ischemic risk factors – diabetes and hypertension and their association with features of stage B heart failure.

Appendix Figures and tables

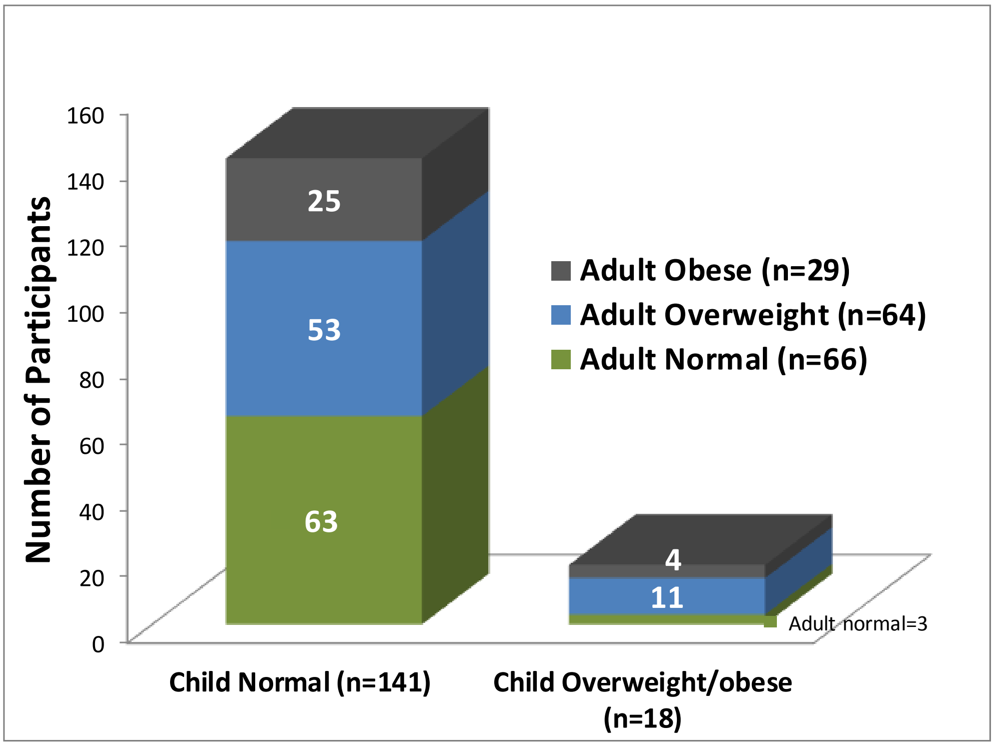


Figure appendix 5.36 -Tracking weight status from childhood to adulthood

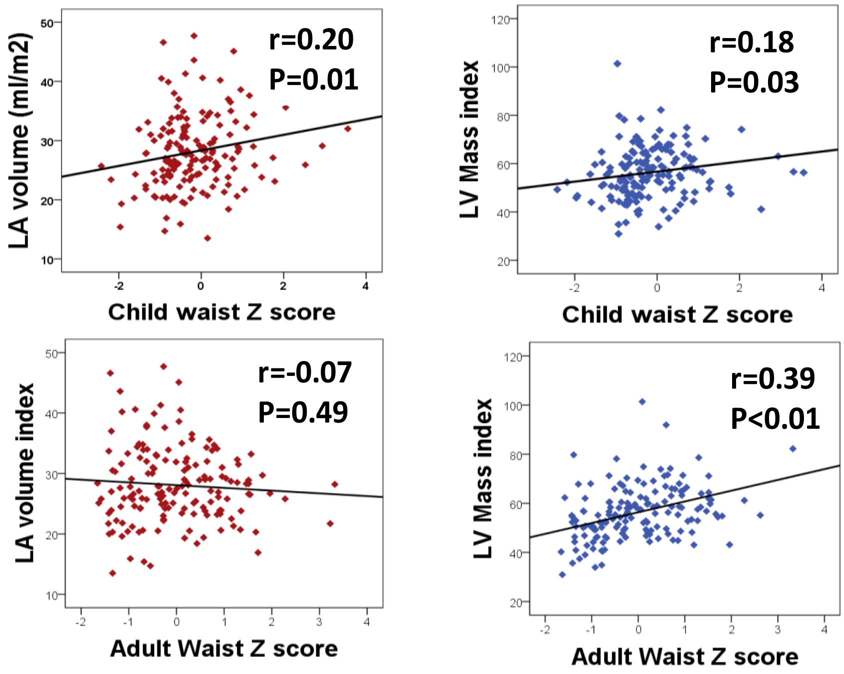


Figure appendix 5.37 -Correlation of waist circumference with cardiac structure
Child waist circumference (WC) correlates with increased LV mass and LA volume. Adult waist circumference (WC) correlates with LV mass but not LA volume.

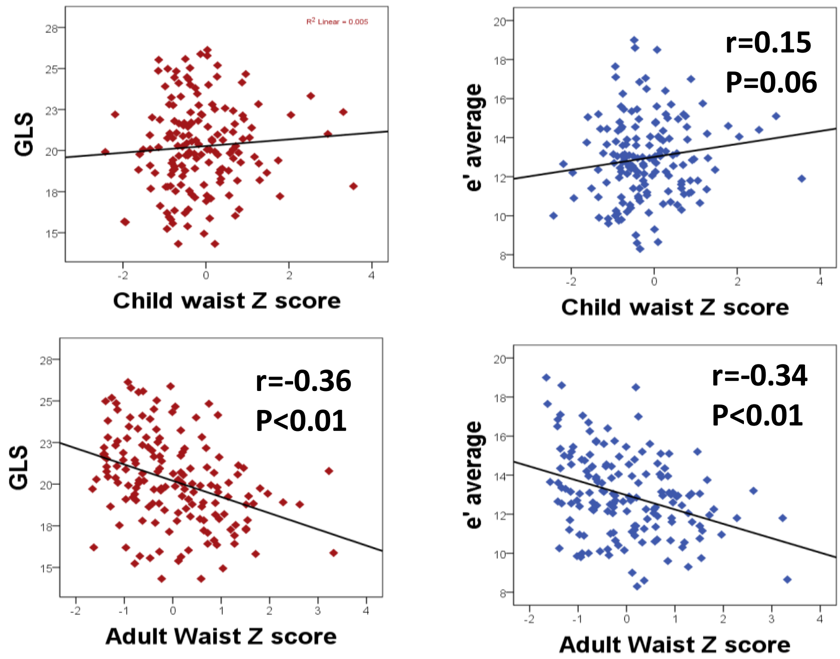


Figure appendix 5.38 -Correlation of waist circumference with cardiac function
Child waist circumference does not correlate with GLS, not with mitral e’
Adult waist circumference correlates with both GLS and mitral e’

Table appendix 5.31 -Correlation of child and adult body adiposity with cardiac structural and function
Body mass index and waist circumference showed stronger association with cardiac structural and functional measures.

	LAVi		**LVMi**		**E/e'**		**e'**		**E/A**		**GLS**	
	r	p value	r	p value	r	p value	r	p value	r	p value	r	p value
Child												
Age	-0.045	0.576	0.095	0.232	0.024	0.771	-0.231	0.004	-0.243	0.002	-0.039	0.626
Height (cm)	0.021	0.794	0.134	0.092	0.045	0.582	-0.242	0.002	-0.268	0.001	-0.035	0.665
Weight (kg)	0.046	0.568	0.18	0.023	0.091	0.258	-0.197	0.013	-0.234	0.003	0.004	0.961
Body Mass Index (g/m2)	0.147	0.066	0.246	0.002	0.098	0.223	0.025	0.755	0.049	0.544	0.046	0.562
Waist circumference (cm)	0.198	0.012	0.177	0.026	0.039	0.630	0.149	0.062	0.112	0.164	0.071	0.374
Hip (cm)	0.057	0.481	0.174	0.026	0.087	0.283	-0.124	0.122	-0.169	0.036	0.040	0.622
Waist-Height ratio	0.130	0.104	0.180	0.024	-0.020	0.809	0.207	0.009	0.127	0.115	-0.014	0.862
Waist-Hip ratio	0.057	0.481	0.140	0.080	-0.133	0.099	0.107	0.184	0.034	0.679	-0.154	0.054
Adult												
Height (cm)	0.140	0.079	0.224	0.004	-0.136	0.090	-0.153	0.055	-0.127	0.114	-0.324	<0.001
Weight (kg)	0.026	0.744	0.381	<0.001	0.085	0.294	-0.305	<0.001	-0.275	0.001	-0.313	<0.001
Body Mass Index (g/m2)	-0.055	0.489	0.342	<0.001	0.194	0.016	-0.289	<0.001	-0.257	0.001	-0.164	0.039
Waist circumference (cm)	-0.071	0.489	0.394	<0.001	0.085	0.293	-0.350	<0.001	-0.336	<0.001	-0.362	<0.001
Hip (cm)	-0.019	0.813	0.293	<0.001	0.176	0.029	-0.222	0.005	-0.165	0.041	-0.083	0.298
Waist-Height ratio	-0.135	0.094	0.350	<0.001	0.151	0.062	-0.323	<0.001	-0.316	<0.001	-0.267	0.001
Waist-Hip ratio	-0.076	0.343	0.334	<0.001	-0.016	0.842	-0.345	<0.001	-0.361	<0.001	-0.474	<0.001

r: correlation coefficient; LAVi: left atrial volume index; LVMi left ventricular mass index; e': mitral annular early diastolic tissue velocity;
E/e': mitral inflow peak early diastolic velocity/mitral annular early diastolic tissue velocity; GLS: global longitudinal strain

Table appendix 5.32 -Relative risk of increased body size

Body size measured as (every one standard deviation change of body mass index [BMI] and Waist circumference [WC]) abnormal cardiac structure and function using conventional cut-offs.

	LA enlargement (34)			LV hypertrophy			Abnormal mitral e'			Impaired GLS		
	R^2	RR (95%CI)	p	R^2	RR (95%CI)	p	R^2	RR (95%CI)	p	R^2	RR (95%CI)	p
Body mass index (BMI)												
Child BMI (adjusted for adult BMI)	0.073	1.81 (1.02, 3.21)	0.04	0.300	2.04 (1.09, 3.78)	0.02	0.140	0.52 (0.22, 1.25)	0.14	0.285	0.46 (0.24, 0.89)	0.02
Adult BMI (adjusted for child BMI)	0.073	0.53 (0.29, 0.97)	0.04	0.300	1.77 (1.13, 2.76)	0.01	0.140	1.31 (0.62, 2.75)	0.48	0.285	1.18 (0.68, 2.08)	0.56
Waist circumference												
Child waist (adjusted for adult waist)	0.141	2.05 (1.26, 3.34)	<0.01	0.253	1.52 (0.94, 2.48)	0.09	0.192	0.35 (0.13, 0.94)	0.04	0.260	0.59 (0.33, 1.08)	0.09
Adult waist (adjusted for child waist)	0.141	0.37 (0.17, 0.80)	0.01	0.253	2.01 (1.18, 3.38)	0.01	0.192	1.71 (0.79, 3.66)	0.17	0.260	1.33 (0.76, 2.31)	0.31

Each model contains age and gender

Cut-offs for LA enlargement: ≥34 ml/m2; LV hypertrophy >95 female, >115 male; Abnormal mitral e’: averaged e’<10 cm/s; Impaired GLS <18%.

Chapter 6

Baseline Cross Sectional Analyses – Association of Aetiology and Pathophysiology

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Hong Yang, Ying Wang, Kazuaki Negishi, Mark Nolan, Thomas H Marwick

Chapter 6. Baseline Cross Sectional Analyses

Pathophysiological Effects of Different Risk Factors for Heart Failure

Introduction

Among the listed stage A heart failure risk factors, not all are equal. The two main non-ischemic risk factors are hypertension and type 2 diabetes and highly prevalent in the community, with 54% having type 2 diabetes and 82% hypertension in the TasELF cohort. As will be described in the following section, many had suboptimal control of their primary risk factors, i.e. >50% hypertensive patients were poorly controlled by their current medication. The early detection of coronary artery disease has a relatively different pathway as most will present with chest pain or angina, therefore the early intervention for cardioprotection of these patients is relatively well defined. Unlike coronary artery disease, the underlying cardiac damage may not be identified, as echocardiography is not indicated in this population. It is unknown whether the underlying cardiac changes are related to etiology. This chapter assessed whether there was association between different risk factors and related pathophysiology.

The following text of this chapter has been published in ***Open Heart 2016;3(1): e000339.***

Abstract

Background. Hypertension and type 2 diabetes mellitus (T2DM) are important causes of non-ischemic heart failure (HF). Understanding the pathophysiology of early HF may guide screening. We hypothesized that the underlying physiology differed according to etiology.

Methods. In this cross-sectional study of 521 asymptomatic community-based subjects ≥65 years with ≥1 HF risk factors, 187 subjects (36%) had both T2DM and hypertension (T2DM+/HTN+), 109 (21%) had T2DM with no hypertension

(T2DM+/HTN-), and 72 (14%) had neither T2DM nor hypertension (T2DM-/HTN-). In 153 (29%), clinic blood pressure was ≥140/90 mmHg, defined as active hypertension (T2DM-/HTN+). All underwent a comprehensive echocardiogram, including conventional parameters for systolic and diastolic function as well as global longitudinal strain (GLS), diastolic strain (DS) and diastolic strain rate (DSR). A six-minute walk test (6MW) was used to assess functional capacity.

Results. GLS in T2DM-/HTN+ group (-18.9±2.7%) was similar to that in T2DM-/HTN- group (-19.4±2.4%), and greater than T2DM+/HTN- (-18.0±2.8%, p=0.005). DS in T2DM-/HTN- (0.47±0.15%) exceeded that in T2DM-/HTN+ (0.43±0.14%) and T2DM+/HTN- (0.43±0.13%). 6MW distance was preserved in T2DM-/HTN+ (482±85m) and reduced in T2DM+/HTN- (469±93, p<0.001). Those with T2DM and active hypertension had worst GLS, DS, DSR and shortest 6MW distance (p<0.002). In multivariable analysis, GLS was associated with T2DM but neither active hypertension nor a history of hypertension. Diastolic markers and LV mass were associated with hypertension and T2DM. Thus, subjects with HF risk factors show different functional disturbances according to aetiology.

Conclusion. Patients with hypertension had relatively less impaired GLS and preserved 6MW distance but more impaired diastolic function.

6.1 Background

The aetiology and pathophysiology of heart failure (HF) is undergoing a transition. With the decline of coronary artery disease (CAD), hypertension and type 2 diabetes mellitus (T2DM) have become the most common aetiologies of incident HF. Among these preclinical individuals with stage A HF[25], the risk of incident HF with hypertension is known to be relatively lower than CAD and T2DM [273], the role of hypertension as the leading cause of HF[274] reflects its prevalence in the community. In contrast, the risk of incident HF is nearly twice as high in those with T2DM [273]. Both conventional echocardiographic measures of diastolic dysfunction and myocardial strain analysis have been well studied in T2DM and are early markers of diabetic cardiomyopathy[275] [57,58]. Unfortunately, the conventional echocardiographic assessment of diastolic function in hypertension often provides inconsistencies [276] which may compromise its use to screen for preclinical HF. A screening and early treatment process could limit the progression to HF arising from the heavy burden of hypertension and T2DM in the community. However, it is not clear whether strain or conventional diastolic measures would be optimal for this purpose, whether they are analogous, or indeed if the underlying ethology has a differential effect on either marker.

6.2 Aims and Hypothesis

An understanding of the pathophysiologic differences of different causes of preclinical HF might guide screening for early intervention and disease prevention. We hypothesised that the optimal cardiac markers vary with the underlying aetiology, and that the degree of underlying cardiac dysfunction correlates with their functional capacity measured by six-minute walk test distance (6MW) – a simple measure of the functional status of patients and as a predictor of morbidity and mortality in LV dysfunction [277].

6.3 Methods

Patient selection. Asymptomatic individuals ≥65 years old with HF risk factors were recruited through local media advertising based on the presence of ≥1 of the following HF risk factors: (1) hypertension (based on self-report of diagnosis including medication); (2) T2DM (based on self-report of diagnosis including medication); (3) obesity (body mass index [BMI] ≥30); (4) previous chemotherapy; (5) family history of HF; (6) previous history of heart disease (but not existing HF). The exclusion criteria were subjects with: (1) a history of previous HF; (2) a history of coronary artery disease CAD (3) a history (or evidence on baseline echocardiogram) of >moderate valvular heart disease; (4) left ventricular ejection fraction <40% on baseline echocardiogram; (5) inability to acquire interpretable images for speckle tracing imaging analysis at baseline. This study was performed in accordance with a research protocol approved by the Tasmanian Human Research Ethics Committee. A written informed consent was obtained from each participant after explained the nature and purposes, complexity and level of risk of the study.

Data collection. Data were collected prospectively at facilities in the community, from all participants enrolled in the study. All completed standard questionnaires relating to health status (EuroQol 5-dimension index, EQ5D), functional capacity (Duke Activity Score Index, DASI), frailty (Study of Osteoporotic Fractures frailty index (SOF)), symptom status (Minnesota Living with HF Questionnaire, MLHFQ). Anthropometric measurements were obtained and body mass index was calculated. Waist and hip measurements were obtained. Standard serial blood pressure measurements, standard 12 lead electrocardiogram (ECG) and a comprehensive transthoracic echocardiogram including speckle tracing imaging was performed. A six-minute walk test (6MW) was used to assess submaximal functional capacity.

Other collected data included socioeconomic indicators, complete medical history, family history, cardiovascular risk factors, heart rate and patient-reported outcome measures.

Blood pressure measurements: Peripheral and derived aortic blood pressure readings were obtained using a validated technique [278], with a commercially available pulse-wave analysis system (Mobil-O-Graph PWA, IEM, Stolberg, DE). Serial measurements were conducted after a 10-minute rest in a quiet room, with readings were obtained twice in a seated position at rest and immediately after 6MW. To define active hypertension, an averaged (at least two) sitting systolic blood pressure (SBP) $\geq$140 mmHg or diastolic blood pressure (DBP) $\geq$90 mmHg were used as cut-off [279,280].

Standard echocardiographic study. Standard transthoracic 2D and Doppler echocardiographic studies were performed using a commercial system (Siemens ACUSON SC2000, 4V1c and 4Z1c probes, Siemens Healthcare, Mountain View, CA) in accordance with the American Society of Echocardiography guidelines [187,281]. Left ventricular (LV) dimensions during diastole and systole and wall thicknesses were measured from parasternal long-axis views according to the recommended criteria. LV mass was calculated according to guidelines and indexed for body surface area (BSA) (g/m^2). LV hypertrophy (LVH) was defined as LV mass index (LVMi) >115 g/m^2 in men and >95 g/m^2 in women [187]. LV and left atrial (LA) volumes were calculated by the Simpson biplane method, and indexed to body surface area (LAVi). Abnormal LAVi was defined as >34 ml/m^2 [187]. For diastolic function assessment, mitral inflow peak early diastolic velocity (E), peak late diastolic velocity (A), E/A ratio, E wave deceleration time (DT) were measured; E/A<0.8 identified delayed relaxation. Tissue

Doppler mitral annular early diastolic velocity (e’) was assessed at septal and lateral walls and averaged for calculation of E/e’; an average E/e’≥15 was considered consistent with raised filling pressure.

Myocardial strain. Speckle tracking was used for measurement of global longitudinal strain (GLS), from 3 standard apical views, using commercial software (Syngo VVI, Siemens Medical Solutions). After manual tracing of LV endocardial border during end-systole, this was automatically tracked throughout the cardiac cycle. GLS was obtained by averaging all 18 segment strain values from the three standard views; abnormal GLS is defined as >-18% [85]. Global diastolic strain was obtained by averaging of all 18 segment strain values and measured according to method published by Ishii et.al. [282]. Calculation of diastolic strain was determined as (A-B)/A * 100% (A= the systolic value of strain at closure of aortic valve; B= the value of strain at the one-third point of diastole duration) (Figure 6.39). Diastolic strain rate was determined from the average of 18 segments of early diastolic strain rate.

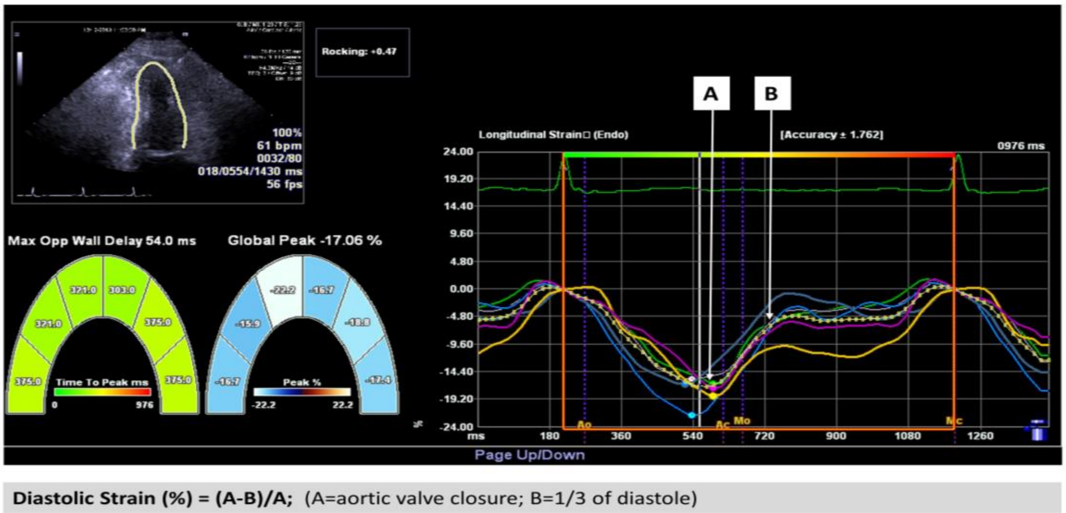


Figure 6.39 Measurement of GLS and diastolic strain (DS)

Functional capacity assessment. A 6-minute walk test distance (6MW) was used for the measurement of sub-maximal functional capacity in this study. 6MW was conducted following a standardized protocol [209].

Statistical analysis. Data are presented as mean ± standard deviation (SD) after testing for normal distribution with the Kolmogorov-Smirnov test. Data deviating from normality are expressed as median and inter-quartile range (IQR). Categorical variables are expressed as percentages. Multi-group comparison was performed by the analysis of variance (ANOVA) with Bonferroni post hoc analysis when data showed a normal distribution. Otherwise, the Kruskal-Wallis test was used for comparison of non-normally distributed variables. Linear regression analysis was used to examine the associations between clinical, echocardiographic and functional variables before and after adjustment for age, gender and other clinical variables. Logistic regression analysis was used to examine the association of low functional capacity and abnormal GLS. Statistical analysis was performed using a standard statistical software package (SPSS software 22.0, SPSS Inc., Chicago, IL). Statistical significance was defined by $p < 0.05$.

6.4 Results

Population characteristics. There were 535 community individuals potentially eligible for assessment during the study period. After exclusion of 14 after the baseline echo screening due to valvular pathology and poor LV ejection fraction, the final number of individuals included in this study was 521 (age 71±5 [IQR: 67-74]) years, 49% of whom were men. All had completed assessment according to the standard protocol. The listed HF risk factors were present in all of these subjects, with self-reported hypertension being the most common (82%), T2DM (54%) and obesity (47%), previous chemotherapy (9.2%), family history of heart disease at young age (36%) and a known cardiac condition without overt HF (10%). All had normal LVEF ($\geq$50%). A total of 340 out of 521 subjects (65%) met the criteria of active hypertension (SBP $\geq$140 mmHg and or DBP $\geq$ 90 mmHg).

Four groups were derived according to the status of T2DM and the presence of hypertension, named T2DM+/HTN-; T2DM/HTN+; T2DM+/HTN+; T2DM-/HTN-. These four etiologic groups were studied to test the individual effect of hypertension versus T2DM and combined effect of T2DM+hypertension (Table 6.33**.** There was no difference in age and gender between T2DM-/HTN+ and T2DM+/HTN-. Other risk factors including obesity, chemotherapy, family history, history of heart disease were also similar between the two groups (Table 6.33). However, compared to T2DM-/HTN+, T2DM+/HTN- had significantly higher prevalence of dyslipidaemia

($p<0.001$) and higher ARIC and FHS scores ($p<0.001$). The T2DM+/HTN+ group had significantly greater body mass index (BMI) and dyslipidaemia. Baseline medication history (including beta blocker (BB), angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), diuretics and calcium antagonists) was similar. A greater percentage of participants with T2DM+/HTN+ were on statin therapy than other groups.

Echocardiographic assessment. Baseline echocardiographic measures stratified by the four etiologic groups are summarized in Table 6.34. LVMi was higher in hypertensive groups (T2DM-/HTN+ and T2DM+/HTN+), but LVEF, LVEDV and RWT were similar among the groups. Of the conventional diastolic parameters, mitral annular e' (average of medial and lateral) was lower and E/e' (average of medial and lateral) was higher in T2DM-/HTN+ and T2DM+/HTN+ than T2DM+/HTN-. Using E/e' >15 as cut-off, the percentage of abnormal E/e' in the groups was different ($p=0.049$). T2DM+/HTN+ had the highest prevalence of diastolic dysfunction (82%) according to the current recommendations of the American Society of Echocardiography [281], although this was not statistically significant among the groups.

Echocardiographic assessment using speckle tracking analysis is also summarized in Table 6.34. GLS was significantly lower in T2DM+/HTN- and T2DM+/HTN+. Using -18% as cut-off, abnormal GLS was present in 42% of the whole cohort, most commonly in those with T2DM (T2DM+/HTN- and T2DM+/HTN+). Diastolic strain and diastolic strain rate were reduced in T2DM-/HTN+, T2DM+/HTN- and T2DM+/HTN+. Comparison of conventional and STE analysis measures among and between four groups are shown in Figure 6.40 A-H**.**

Association of hypertension and T2DM with cardiac changes. The association between abnormal functional parameters and T2DM and hypertension were tested using univariable analysis, followed by two multivariable models to test the independent association between T2DM, a history of hypertension and active hypertension (the latter two being entered into each model separately (Table 6.35). When modelled with age, gender, BMI and HR, reduced GLS was independently associated with T2DM but not hypertension (either history or active). In contrast, diastolic parameters were generally associated with active hypertension as well as T2DM.

Table 6.33 Baseline demographic and clinical characteristics by etiology

	Total (n=521)	**T2DM-/HTN+ (n=153)**	p (HTN-contrl)	**T2DM+/HTN- (n=109)**	p (T2DM-contrl)	p (HTN-T2DM)	**T2DM+/HTN+ (n=187)**	p (Both-contrl)	p (Both-HTN)	p (Both-T2DM)	**T2DM-/HTN- (n=72)**	**p (total)**
Age (years)	71 (5)	71 (5)		71 (4)			71 (5)				71 (5)	0.742
Gender male, n (%)	256 (49)	65 (43)	0.478	59 (54)	0.028	0.063	105 (56)	0.007	0.012	0.736	27 (38)	0.010
Heart rate (bpm)	67 (59-75)	66 (58-74)	>0.99	68 (60-76)	0.102	0.324	68 (61-75)	0.162	0.530	>0.99	64 (59-72)	0.035
SBP (mmHg)	146 (18)	156 (15)	<0.001	130 (8)	>0.99	<0.001	154 (14)	<0.001	0.460	<0.001	128 (10)	<0.001
DBP (mmHg)	82 (11)	90 (11)	<0.001	74 (7)	>0.99	<0.001	84 (10)	<0.001	0.315	<0.001	74 (7)	<0.001
Pulse pressure (mmHg)	64 (15)	67 (15)	<0.001	55 (8)	>0.99	<0.001	69 (15)	<0.001	0.324	<0.001	54 (12)	<0.001
Mean artery pressure	108 (12)	114 (13)	<0.001	99 (7)	>0.99	<0.001	111 (9)	<0.001	0.149	<0.001	100 (9)	<0.001
Central SBP (mmHg)	149 (20)	158 (20)	<0.001	131 (13)	0.947	<0.001	154 (18)	<0.001	0.451	<0.001	138 (15)	<0.001
Central DBP (mmHg)	83 (10)	87 (11)	<0.001	78 (6)	>0.99	<0.001	85 (9)	<0.001	0.215	<0.001	77 (9)	<0.001
ΔSBP (pre-post 6MW)	18 (20)	18 (24)		20 (19)	0.392	<0.001	18 (19)				16 (16)	0.722
Body Mass Index (g/m2)	29 (26-33)	29 (26-32)	>0.99	28 (26-32)	>0.99	>0.99	31 (27-34)	0.005	0.050	0.032	28 (25-31)	0.002
HF risk factors												
ARIC risk (4yr) (%)	6.2 (3.6-11.4)	4.2 (2.5-7.3)	0.104	7.3 (4.6-11.9)	<0.001	<0.001	9.2 (6.2-14.9)	<0.001	<0.001	0.048	3.2 (1.8-4.9)	<0.001
FHS risk (4yr) (%)	4.0 (2.0-6.5)	3.0 (2-4)	0.186	4.0 (3-10)	<0.001	<0.001	5.0 (3-14)	<0.001	<0.001	1.000	2.5 (1.8-3)	<0.001
T2DM, n (%)	296 (57)	0 (0)	n/a	109 (100)	<0.001	<0.001	187 (100)	<0.001	<0.001	n/a	0 (0)	<0.001
Obesity, n (%)	245 (47)	67 (44)	0.197	46 (42)	0.313	0.798	107 (57)	0.001	0.014	0.013	25 (35)	0.003
History HTN, n (%)	421 (81)	134 (88)	0.556	75 (67)	0.015	<0.001	151 (81)	0.457	0.089	0.020	61 (85)	0.002
Chemotherapy, n (%)	46 (9)	13 (9)	0.529	7 (6)	0.263	0.533	18 (10)	0.722	0.719	0.339	8 (11)	0.701
Family History, n (%)	184 (35)	63 (41)	0.944	44 (40)	0.862	0.895	47 (25)	0.009	0.002	0.006	30 (42)	0.004
History heart dis, n (%)	47 (9)	21 (14)	0.011	9 (8)	0.131	0.171	15 (8)	0.127	0.089	0.943	2 (3)	0.049
Dyslipidaemia, n (%)	284 (55)	60 (41)	0.580	64 (63)	<0.001	<0.001	121 (72)	0.018	<0.001	0.159	39 (56)	<0.001
Charlson score	1.0 (0.0-2.0)	0 (0-1)	1.000	1.0 (1-3)	<0.001	<0.001	1.0 (1-2)	<0.001	<0.001	1.000	0 (0-1)	<0.001
Medication, n (%)												
Beta blocker	38 (7)	12 (7.8)		11 (10)			10 (5.3)				5 (6.9)	0.495
ACEi/ARB	360 (69)	104 (68)		69 (63)			137 (73)				50 (69)	0.344
Diuretics	67 (13)	22 (16)		11 (11)			21 (13)				13 (19)	0.432
Calcium antagonist	115 (22)	26 (19)		24 (25)			47 (28)				18 (27)	0.273
Lipid Lowering Meds	287 (55)	57 (41)	0.580	75 (76)	<0.001		125 (75)	<0.001	<0.001	0.933	30 (45)	<0.001
Anti-platelet	193 (37)	44 (32)	0.163	41 (41)	0.961		80 (49)	0.334	0.003	0.246	28 (42)	0.031
Functional Capacity												
6MW (meter)	463 (101)	482 (85)	>0.99	469 (93)	>0.99	>0.99	438 (119)	0.019	<0.001	0.067	479 (81)	<0.001
Patient reporting outcome measure												
DASI MET	8.3 (1.0-8.9)	8.9 (7.6-9.0)	>0.99	8.0 (6.6-9.0)	0.036	0.053	7.7 (6.6-9.0)	<0.001	<0.001	>0.99	8.9 (8.0-9.0)	<0.001
EQ5D	0.84 (0.74-1.0)	0.84 (0.77-1.0)	>0.99	0.84 (0.72-1.0)	0.144	0.177	0.81 (0.73-1.0)	0.039	0.027	>0.99	0.88 (0.77-1)	0.004
EQ VAS	80 (70-90)	85 (70-93)	>0.99	80 (70-90)	0.029	0.202	80 (70-90)	0.024	0.179	>0.99	88 (79-95)	0.005

MLHF	1.0 (0.0-9.0)	1.0 (0-7)	1.0 (0-9.5)	1.0 (0-12)	1.0 (0-6.8)	0.971

Continuous variables are listed either: mean (SD) or median (low quartile-upper quartile); Categorical variables are listed: number (%); ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blockers ARIC: The Atherosclerosis Risk in communities; Both=HTN+/T2DM+; Contrl=HTN-/T2DM-; DASI MET: Duke Activity score index with metabolic equivalent task; DBP: diastolic blood pressure; EQ5D: European Quality of Life-5 dimensions; EQVAS: European Quality of Life visual analogue scale; FHS: Framingham Heart Study; HTN: hypertension; MLHF: Minnesota Living with Heart Failure score; PROMs: patient reporting outcome measures; SBP: systolic blood pressure; T2DM: type 2 diabetes mellitus; 6MW: six-minute walk test

Table 6.34 Echocardiographic characteristics of patients

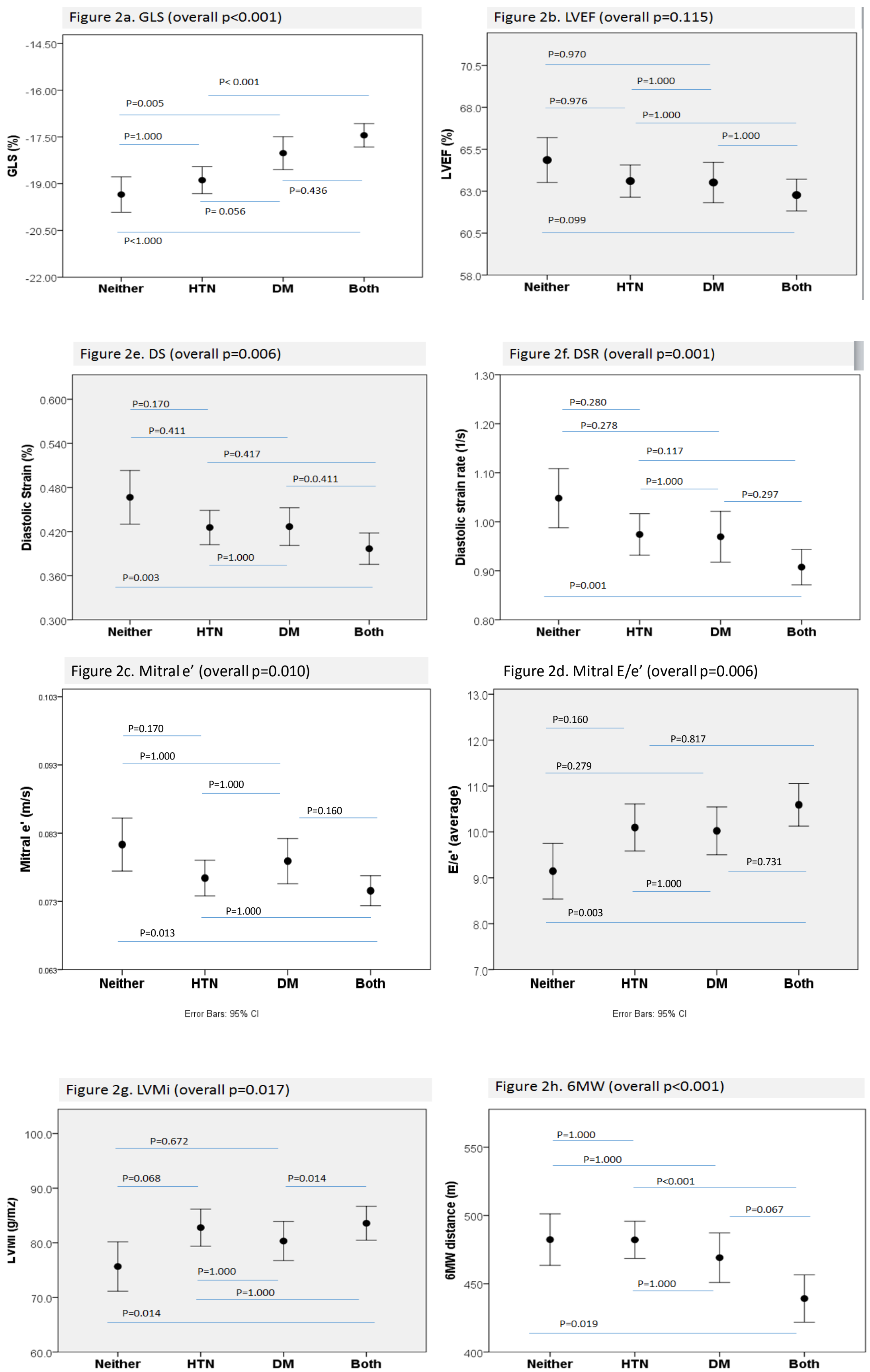
Echocardiographic characteristics of patients with stage A heart failure, categorized by aetiology

	Total (n=521)	**T2DM-/HTN+ (n=153)**	p (HTN-Contrl)	**T2DM+/HTN- (n=109)**	p (T2DM-Contrl)	p (HTN-T2DM)	**T2DM+/HTN+ (n=187)**	p (Both-contrl)	P (HTN-both)	p (T2DM-both)	**T2DM-/HTN- (n=72)**	**p (total)**
LVIDd	4.6 (0.6)	4.6 (0.6)		4.6 (0.5)			4.6 (0.6)				4.5 (0.5)	0.376
LVEDV (2D) (ml)	88 (26)	88 (22)		85 (25)			91 (27)				86 (28)	0.189
LVEF (%)	63 (6)	64 (6)		64 (6)			63 (7)				65 (6)	0.115
RWT	0.43 (0.1)	0.43 (0.1)		0.43 (0.1)			0.44 (0.1)				0.42 (0.1)	0.289
GLS (%)	-18.3 (2.7)	-18.9 (3)	>0.99	-18.0 (3)	0.005	0.056	-17.4 (3)	<0.01	<0.01	0.436	-19.4 (2)	<0.01
Abnormal GLS, n (%)	220 (42)	50(33)		51 (47)			102 (55)				17 (24)	<0.01
DD (Grade_0), n (%)	102 (20)	32 (21)		23 (21)			30 (16)				17 (24)	
DD (Grade_I), n (%)	298 (57)	87 (57)		58 (53)			116 (62)				37 (51)	0.649
DD (Grade_II), n (%)	100 (19)	27 (18)		21 (19)			36 (19)				16 (22)	
E/A	0.8 (0.2)	0.80 (0.2)		0.82 (0.21)			0.78 (0.20)				0.83 (0.18)	0.203
DT (ms)	249 (51)	247 (54)		248 (53)			253 (52)				245 (39)	0.597
e' (cm/s)	7.7 (1.6)	7.6 (1.6)	0.170	7.9 (1.7)	>0.99	>0.99	7.5 (1.5)	0.013	1.000	0.160	8.2 (1.6)	0.010
E/e'	10.1 (3)	10.1 (3.2)	0.135	10.0 (2.7)	0.279	>0.99	10.6 (3.2)	0.003	0.817	0.731	9.1 (2.6)	0.006
Preclinical HF (E/e'15) (n, %)	70 (13)	22 (14)		11 (10)			33 (20)				4 (6)	0.049
Diastolic Strain (%)	0.41 (0.15)	0.43 (0.15)	0.278	0.43 (0.13)	0.411	>0.99	0.39 (0.15)	0.003	0.417	0.411	0.47 (0.15)	0.006
Diastolic SR (1/s)	0.96 (0.26)	0.97 (0.26)	0.280	0.97 (0.27)	0.278	>0.99	0.91 (0.25)	0.001	0.117	0.297	1.05 (0.25)	0.001
LAVi (ml/m2)	31 (10)	31 (10)		31 (10)			33 (10)				30 (10)	0.148
LVMi (g/m2)	93 (24)	96 (22)	0.023	88 (21)	>0.99	0.033	96 (26)	0.017	>0.99	0.024	86 (21)	0.001
Preclinical HF (LVH) (n, %)	143 (27)	58 (38)		16 (15)			58 (31)				11 (15)	<0.01

Continuous variables are listed as mean (SD); Categorical variables are listed as number (%).
Both=HTN+/T2DM+; Contrl=HTN-/T2DM-; HTN: hypertension; T2DM: type 2 diabetes mellitus;
LVIDd: left ventricular internal dimension during end diastole; LVEDV: left ventricular end diastolic volume; LVEF: left ventricular ejection fraction; RWT: relative wall thickness; GLS: global longitudinal strain;
DD: diastolic dysfunction grading according to ASE recommendation; LAVi: left atrium volume index; LVMi left ventricular mass index; LVH: left ventricular hypertrophy

Association of exercise capacity with cardiac changes in hypertension and T2DM. The 6MW test distance in the entire cohort correlated with GLS (r=-0.11, p=0.01) and E/e' (r=-0.10, p=0.03), but not other diastolic parameters or LV mass. 6MW distance in subgroups is shown in Figure 6.40H. Compared with T2DM-/HTN-, T2DM-/HTN+ had preserved 6MW distance, while T2DM+/HTN-had a non-significant reduction and those T2DM+/HTN+ had significantly lower 6MW distance (p=0.019). Multivariable analysis showed T2DM was independently associated with reduced 6MW in both models (history of hypertension and active hypertension). In contrast, active or history of hypertension was associated with preserved 6MW after adjustment for age, gender, height, SBP and heart rate (Table 6.36).

Lastly, Table 6.37 summarizes the association of 6MW distance with abnormal cardiac functional parameters, after adjusting for age, gender, height, HR and SBP. 6MW was independently associated with GLS, DS and LVMi, not with other diastolic parameters. In multivariable logistic analysis using GLS (-18% cut-off) and 6MW (lower quartile distance: 410 cut-off), those with 6MW distance <410 meters were associated with abnormal GLS with an odds ratio of 1.69 (95% CI: 1.09- 2.60, p=0.02).



Abnormal strain (2A) but not EF (2B). Diastolic markers (2C-F), LV mass (2G) and exercise capacity (2H) were impaired in the presence of both hypertension and T2DM.

Figure 6.40 Association of LV function with hypertension and T2DM.

Table 6.35 Association of T2DM and hypertension with cardiac function

	GLS		DS		DSR		e'		E/e'		E/A		LVMi	
	ß (95% CI)	p	ß (95% CI)	p	ß (95% CI)	p	ß (95% CI)	p	ß (95% CI)	p	ß (95% CI)	p	ß (95% CI)	p
Univariate analysis														
T2DM	1.383 (0.922, 1.845)	<0.001	-0.031 (-0.056, -0.01)	0.017	-0.068 (-0.11, -0.022)	0.004	-0.002 (-0.005, 0.001)	0.191	0.603 (0.073, 1.134)	0.026	-0.015 (-0.051, 0.020)	0.396	0.097 (-3.99, 4.19)	0.963
History HTN	-0.156 (-0.755, 0.443)	0.608	-0.007 (-0.040, 0.025)	0.649	-0.012 (-0.07, 0.046)	0.679	-0.002 (-0.006, 0.001)	0.214	0.689 (0.021, 1.357)	0.043	0.011 (-0.034, 0.057)	0.622	5.82 (0.695, 10.94)	0.026
Active HTN	0.463 (-0.031, 0.957)	0.066	-0.033 (-0.06, -0.007)	0.014	-0.063 (-0.11, -0.016)	0.009	-0.005 (-0.007, -0.002)	0.002	0.711 (0.160, 1.262)	0.012	-0.037 (-0.074, 0.001)	0.053	8.72 (4.53, 12.92)	<0.001
Model with history of HTN*														
T2DM	0.972 (0.522, 1.423)	<0.001	-0.021 -0.043, 0.000)	0.054	-0.062 (-0.11, -0.015)	0.010	-0.003 (-0.006, -0.001)	0.020	0.764 (0.229, 1.298)	0.005	-0.000 (-0.025, 0.035)	0.996	-1.553 (-5/43, 2.321)	0.431
History HTN	-0.025 (-0.578, 0.529)	0.931	-0.015 (-0.042, 0.012)	0.275	-0.016 (-0.073, 0.042)	0.590	-0.002 (-0.006, 0.001)	0.164	0.742 (0.086, 1.399)	0.027	0.011 (-0.032, 0.055)	0.615	4.26 (-0.493, 9.02)	0.098
Model with active HTN*														
T2DM	1.00 (0.56, 1.45)	<0.001	-0.022 (-0.04, -0.001)	0.044	-0.064 (-0.11, -0.02)	0.010	-0.003 (-0.006, -0.001)	0.017	0.726 (0.19, 1.26)	0.007	-0.003 (-0.04, 0.03)	0.848	-1.564 (-5.375, 2.247)	0.421
Active HTN	0.408 (-0.05, 0.86)	0.079	-0.035 (-0.06, -0.013)	0.002	-0.059 (-0.11, -0.013)	0.013	-0.005 (-0.007, -0.002)	0.001	0.691 (0.151, 1.23)	0.012	-0.033 (-0.069,0.032)	0.848	7.029 (3.144, 10.91)	<0.001

* adjusted for age, male gender, BMI, HR

GLS: global longitudinal strain; DS: diastolic strain; DSR: diastolic strain rate; LVMi: left ventricular mass index; T2DM: type 2 diabetes mellitus; HTN: hypertension

Table 6.36 Association of 6MW distance with hypertension and T2DM status

	Univariable analysis			Model with history of hypertension			Model with active hypertension		
	r^2	ß (95% CI)	p value	ß (95% CI)	r^2	p value	ß (95% CI)	p value	r^2
Age	0.090	-6.314 (-8.06, -4.56)	<0.001						
Male gender	0.023	30.8 (13.4, 48.1)	0.001						
BMI	0.050	2.274 (1.41, 3.14)	<0.001						
SBP	0.017	-0.742 (-1.24, -0.25)	0.003						0.181
HR	0.029	-1.559 (-2.345, -0.773)	<0.001		0.182				
T2DM	0.024	-31.66 (-49.1, -14.2)	<0.001	-34.5 (-51.2, -17.8)		<0.001	-35.29 (-51.8, -18.7)	<0.001	
History HTN	0.000	2.72 (-19.44, 24.88)	0.810	7.056 (-13.9, 28.0)		0.508		0.687	
Active HTN	0.005	-15.14 (-33.56, 3.28)	0.107				-4.88 (-28.7, 18.9)		

SBP: systolic blood pressure; HR: heart rate; T2DM: type 2 diabetes mellitus; HTN: hypertension

Table 6.37 Association of 6MW with echocardiographic measures

	r^2	ß (95% CI)	p value
GLS*	0.142	-0.281 (-0.52, 0.04)	0.002
DS*	0.339	-0.015 (-0.03, 0.004)	0.010
DSR*	0.052	-0.001 (-0.03, 0.02)	0.930
e'*	0.125	-0.001 (-0.003, 0.0001)	0.072
E/e'*	0.083	0.002 (-0.28, 0.28)	0.988
E/A*	0.109	-0.005 (-0.02, 0.01)	0.610
LVMi*	0.171	-1.826 (-3.58, -0.08)	0.041

*adjusted with age, gender, height, HR, SBP.
Beta as per 100 meter distance of 6MW test.

6.5 Discussion

This study demonstrated that in individuals with non-ischemic stage A HF risks, T2DM is associated with more impaired cardiac function and reduced exercise capacity than is present in those with hypertension. Although patients with both well- and poorly-controlled blood pressure showed abnormal diastolic function, it appears that abnormal GLS is an independent marker for diabetic cardiomyopathy rather than hypertensive heart disease. Poor BP control is associated with more impaired cardiac function with or without the presence of diabetes.

Combined effect of T2DM and hypertension on LV function. Diabetes and hypertension constitute two powerful independent risk factors for cardiovascular disease. T2DM is known to be a strong predictor of incident HF, independent of other concomitant risk factors [57,65,283-286]. Subclinical diastolic dysfunction and systolic impairment assessed using global longitudinal strain (GLS) are believed to be early markers of diabetic cardiomyopathy [58,65]. However, hypertension is present in 40-80% of patient with longstanding diabetes [287] and most of these studies were performed in populations with a high prevalence of hypertension, and therefore reflect the combined impact of hypertension and T2DM. In our study, patients with mixed T2DM and hypertension had a 20% prevalence of E/e’>15, analogous to a 23% prevalence in another community-based study of 1760 T2DM patients with an 86% of hypertension and 36% of prevalence of coronary artery disease (CAD). Follow-up of that group showed that the hazard ratio (HR) of hypertension (HR 4.27, 95%CI 1.92-12.15) for subsequent HF was almost double that of CAD (HR 2.2, 95% CI 1.62-3.01). The negative synergistic effect of hypertension and diabetes was likely the cause of high prevalence of impaired diastolic and systolic dysfunction and associated adverse outcome [288] [57,65]. However, the exact underlying pathophysiology of this combined impact is unclear. Diabetes is a metabolic disorder characterized by intracellular accumulation of toxic fatty acid intermediates [289]. This change also affects cardiac mitochondrial resulting in contractile dysfunction [290]. There is a well-recognized tendency to develop diastolic dysfunction even in the absence of significant hypertension, however, the presence of hypertension may accelerate the adverse changes and cause end organ damage [291]. Quantitative measure using fibrosis score showed the degree of myocardial and interstitial fibrosis contributes to the pathological involvement [292]. The score was found to be lowest for hypertensive, midrange for diabetic and highest for hypertensive-diabetic. It is presumed that fibrosis and metabolic consequences of myocyte in diabetes leading to impaired both systolic and diastolic function, while chronic afterload causing interstitial fibrosis lead to a more impaired diastolic than systolic function in hypertension. The coexisting hypertension exacerbates functional changes by producing larger amount of fibrosis. Another observation was described that abnormal GLS and diastolic dysfunction were not analogous to each other. As an early marker, diastolic function was documented in 47% of patients with T2DM, Ernande showed abnormal strain in 28% of those with normal diastolic function [58]. In multivariable analysis, a history of hypertension but not T2DM was associated with diastolic parameters. This relationship was mirrored in our study, in which the prevalence of diastolic dysfunction was 72% in those with T2DM with abnormal strain in 47% of them (Table 6.34) – a higher prevalence found in our study was likely due to older age (71±5 vs 52±5 years) and higher prevalence of history of hypertension (67% vs 38%). A history of hypertension but controlled blood pressure was associated with increased E/e’, which may represent a combined impact. The findings parallel the finding that hypertension (either historical or high blood pressure at the time of the echocardiogram) was independently associated with e’ and E/e’ and diabetes was associated with E/e’ [288].

It needs to be noted that our finding of GLS was consistently associated with diabetes but not hypertension in the multivariable analysis should not be interpreted as a normal GLS in this population. Influence of afterload on left ventricular causing reduced global longitudinal strain in early disease stage has been describe in both animal model and human studies [248,293,294]. Understanding these difference would be important and beneficial to guide effective screening and early intervention in the community as hypertension and diabetes are the two leading etiology of preclinical HF in this population.

Effects of controlled and uncontrolled hypertension on LV impairment. Hypertension has been shown to precede the development of HF in both men and women [295]. Although there have been improvements in the overall management of hypertension, there remain a significant number of hypertensive patients who remain untreated or fail to achieve optimal control[296,297]. Of the 82% with a known history of hypertension in our study, 92% of them were on anti-hypertensive therapy, but only 33% had good control of blood pressure (Table 6.33). Our study demonstrated uncontrolled blood pressure was independently associated with more severe cardiac dysfunction including abnormal e', E/e', diastolic strain, diastolic strain rate and LV mass. However, GLS appeared to be relatively preserved in those with hypertension as compared to those with neither hypertension and nor T2DM. These findings are inconsistent with previous work in a small group of younger (46±14 years) hypertensive subjects with controlled blood pressure showing lower peak strain and strain rate at rest, with blunting of strain increment during exercise[248]. The dependence of myocardial strain on hemodynamic conditions has been reported in both hypertension[298] [299] and valve disease[300].

Assessment of exercise capacity using 6MW. Impaired exercise capacity and functional changes during exercise were known to be early markers of subclinical LV dysfunction in patients with hypertension and diabetes [70,301,302]. However, a standard exercise testing protocol is not feasible in community-based screening for subclinical LV dysfunction. Due to its simplicity and inexpensiveness, the 6MW test is often used to estimate submaximal functional capacity in this setting; the predictive value of 6MW for peak oxygen uptake is of moderate accuracy [303]. In our study, 6MW distance correlated with subclinical cardiac dysfunction, and was significantly reduced in those with T2DM+/HTN+ individuals, but relatively preserved in those with hypertension alone.

6.6 Study Limitations

The present analysis was based on a cross-sectional sample from a clinical trial population of ≥65-year-old participants with at least one of the listed non-ischemic SAHF risks. The control group without T2DM or hypertension had other HF risks (mainly obesity), but there were no age-matched controls without HF risk factors. Another important limitation of this study was the concomitant presence of coronary artery disease (CAD) was not assessed. Our intention and focus was on non-ischemic population with a very low prevalence of known CAD (<5%). However, diabetic cardiomyopathy and hypertensive heart disease are both known as part of atherosclerosis process, which make their heart susceptible to ischemia coronary changes. Some of the functional changed may be caused by underlying ischemic and non-ischemic pathophysiologic changes. A possible approach to address this limitation would be a stress test to identify those with underlying CAD, but we could not perform this in the context of a community-based study.

6.7 Conclusions

Hypertension is associated with less impairment of GLS and exercise capacity than is T2DM. Those with both well- and poorly-controlled blood pressure showed abnormal diastolic functional markers, and more severely impaired cardiac function was associated with worse BP control. However, GLS appears to be associated with diabetic cardiomyopathy rather than hypertensive heart disease in this population at risk of HF.

Postscript

Findings from this chapter suggest early markers for isolated hypertension and diabetes may be different although these two often coexist. In the community setting, individuals with both comorbidities had more impaired cardiac function.

Next chapter will discuss the role of ECG in screening. ECG is widely used in primary setting. However, it is not sensitive to subtle cardiac changes. We will discuss the role of new ECG markers in relation to echo features and outcome.

Chapter 7

How to Screen – Role of ECG Techniques in Screening

Article "Association between Electrocardiographic and Echocardiographic Markers of Stage B Heart Failure and Cardiovascular Outcome" was published in

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Hong Yang, Thomas H Marwick, Ying Wang, Mark Nolan, Kazuaki Negishi, Faisal Khan, Peter M Okin

Chapter 7. Association between ECG and echo markers and outcome

Role of electrocardiography (ECG) technique in Screening

Introduction

The main concern of community screening using echocardiography is test feasibility and cost. ECG has been widely used as the first line diagnostic tool in primary care to assess cardiac rhythms and ischemic cardiac disease. The potential role of the ECG to screen for non-ischemic stage B heart failure is the focus of this chapter. The TasELF cohort excluded patients with a previous history of valvular disease, coronary artery disease and atrial fibrillation. It was assumed that the main ECG changes would relate to left ventricular hypertrophy, abnormal left atria, QRS duration and minor ST changes. The availability of automated measurement of all ECG markers would also facilitate a comprehensive and multi-marker approach for efficient and effective screening.

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Abstract

Aims. The detection of non-ischemic stage B heart failure (SBHF) may facilitate the recognition of those at risk of progression to overt HF and HF prevention. We sought the relationship of specific electrocardiographic (ECG) markers of SBHF to echocardiographic features of SBHF and their prognostic value for development of HF. The ECG markers were Cornell Product (Cornell-P), P wave terminal force in lead V1 (PTFV1), ST depression in lead V5 V6 (minSTmV5V6) and increased heart rate. Echocardiographic assessment of SBHF included left ventricular hypertrophy (LVH), impaired global longitudinal strain (GLS), and diastolic dysfunction (DD).

Method and results – Asymptomatic subjects ≥65 years without prior cardiac history, but with HF risks, were recruited from the local community. At baseline, they underwent clinical assessment, 12-lead ECG and comprehensive echocardiography. New HF was assessed clinically at mean follow-up of 14±4 months, and echocardiography was repeated in subjects with HF. Of the 447 subjects (age 71±5, 47% men), SBHF was present in 13% by LVH, 31% by impaired GLS and 62% by ≥ grade I DD. Forty were lost to follow-up. Clinical HF developed in 47 of 407, of whom 20% had echocardiographic LVH, 51% abnormal GLS, and 76% DD at baseline. Baseline LVH and abnormal GLS (not grade I DD) were independently associated with outcomes (clinical HF and cardiovascular death). Cornell-P and heart rate (not minSTmV5V6 nor PTFV1) were independently associated with LVH, impaired GLS and DD. Cornell-P and minSTV5V6 (not heart rate nor PTFV1) were independently associated with outcomes. More ECG abnormalities improved sensitivity, but ECG-markers were not independent of or incremental to echocardiographic markers to predict HF in SBHF.

Conclusion – In this elderly study population, ECG markers showed low diagnostic sensitivity for non-ischaemic SBHF and low prognostic value for outcomes. Cornell-P and minSTmV5V6 had predictive value for outcomes in non-ischaemic SBHF independent of age, gender, and common comorbidities but were not incremental to echocardiography.

7.1 Background

Stage B heart failure (SBHF) is an early stage with no symptoms despite evidence of cardiac structural or functional impairment[25,70]. Most often it is due to loss of functioning myocytes from myocardial infarction, valvular disease or left ventricular hypertrophy (LVH) secondary to hypertension[25]. Randomized trials have shown that early intervention can prevent or delay the onset of overt HF in patients with reduced left ventricular ejection fraction (LVEF) in the ischaemic population [37,40]. However, evidence is missing in the non-ischaemic population with preserved LVEF about utility of early diagnosis and treatment. Using echocardiography, SBHF may be detected by LVH, diastolic dysfunction (DD), or impaired global longitudinal systolic strain (GLS)[70]. The assessment of left ventricular (LV) function has been strengthened by speckle-tracking echocardiography. This semi-automated method is highly sensitive for the detection of subtle myocardial impairment, provides incremental prognostic value over LVEF[65] and can be a functional marker of SBHF [70,307]. However, the cost and feasibility of current echocardiographic techniques are a barrier to community-based screening for SBHF. A selective screening strategy of identifying high-risk individuals based on the use of simpler tools that are more feasible could improve the efficiency of a screening approach.

The association of abnormal electrocardiographic (ECG) markers and incident HF has been reported in the literature, including abnormal QRS duration[304], abnormal P-wave terminal force in lead V1(PTFV1)[199], ST changes [198] and various markers in combination [305, 343]. ECG-LVH has been associated with abnormal cardiac function and has predictive value for incident HF independent of echocardiographic LVH [306]. ECG-LVH by Cornell product (Cornell-P) criteria is strongly associated with DD [309], and in a larger cohort of hypertensive patients, ECG-LVH was associated with increased risk of LV systolic dysfunction [310], especially when combined with ST depression in the lateral precordial leads (V5-V6), even in the absence of coronary disease [198, 344]. ECG markers [Cornell-P, PTFV1, minimal ST deviation at m point of leads V5 and V6 (minSTmV5V6), and abnormally increased heart rate] may reflect underlying structural changes in the heart. Their associations with outcome have not been well studied.

7.2 Aims and Objectives

Accordingly, we aimed to evaluate the performance of commonly utilized ECG markers to predict echocardiographic features of SBHF[70] and to compare the prognostic and incremental value of these ECG markers with echocardiographic indices for HF in this community population at risk of HF.

7.3 Methods

Study Population. Participants were enrolled through local media advertising. Data were prospectively collected from subjects ≥65 years old and living in the community. Inclusion was based on the presence of one or more of HF risk factors: 1) hypertension (based on SBP >140 mmHg and/or self-report of anti-hypertensive medication); 2) type 2 diabetes mellitus (T2DM, based on self-report of diagnosis including medication); 3) obesity (body mass index [BMI] ≥30); 4) previous potentially cardio toxic chemotherapy; 5) family history of heart failure; 6) previous history of heart disease (but not existing heart failure). Exclusion was based on subjects with: 1) symptoms or a known history of HF; 2) known coronary artery disease (CAD) including history of myocardial infarction and coronary artery by-pass graft; 3) more than moderate valvular heart disease; 4) reduced LVEF (<40%) on baseline echocardiography; 5) atrial fibrillation (AF); 6) inability to acquire interpretable images at baseline. This study was performed in accordance with a research protocol approved by the Tasmanian Human Research Ethics Committee (HREC), and registered with the Australian and New Zealand Clinical Trials Registry (http://www.anzctr.org.au/ ; ACTRN12614000080628). Individual written informed consent was obtained from participants

Data collection. Data were prospectively collected at facilities in the community, from all participants enrolled in the study. All underwent a physical examination and symptom questionnaire. Anthropometric measurements were obtained and body mass index (BMI) was calculated (body weight [kg]/height^2 [m^2]). Blood pressure was measured twice after 10-minutes of rest. Data were also collected on socioeconomic indicators, complete medical history, and family history. Charlson comorbidity score index was used for comorbidity assessment[311].

Electrocardiogram (ECG). A standard 12-lead ECG was recorded at 25 mm/s and 1 mV/cm according to standard protocol. ECG measurements were performed using MUSE software (GE Healthcare, Milwaukee, WI, USA) including QRS duration and axis, PR, QT and heart rate. Cornell voltage (Cornell-V) was measured as SV3+RaVL and criteria for LVH was defined as ≥2.8 mV (28 mm) in men and ≥2.0 mV (20 mm) in women[310]. Criteria for LVH using the Cornell product (Cornell-P, the product of QRS duration times Cornell voltage [RaVL+SV3] plus 6 mm in women) was defined as ≥ 2440 mm·ms[310], and the 75th percentile of gender specific cut-offs for Cornell-P from the current study population were also used as categorical cut-off. Sokolow-Lyon voltage (SLV) was measured as SV1+RV5 or RV6, and criteria for LVH was defined as ≥3.5 mV (35 mm) [197]. The cut-off for absolute ST segment deviation (minSTmV5V6, the midpoint of the ST segment on median complexes in leads V5 and V6) was defined as <-20uV. Abnormal P-wave terminal force in the right precordial lead V1 (PTFV1; the product of the negative P-wave deflection from onset of the negative deflection to its nadir in lead V1 [uV] and the duration [ms]) was defined as ≤ -4000 uVms [199]. An abnormal ECG was defined as the combination of ≥1 of the following: 1) resting heart rate ≥80 bpm; 2) 75th percentile of Cornel-P; 3) abnormal minSTmV5V6 and 4) abnormal PTFV1.

Echocardiographic study. Standard transthoracic 2D and Doppler echocardiographic studies were performed using standard equipment (Siemens ACUSON SC2000, Siemens Healthcare, Mountain View, CA) and transducer (4V1c, 1.25-4.5 MHz; 4Z1c, 1.5-3.5 MHz) in accordance with the American Society of Echocardiography (ASE) guidelines[187]. LV dimensions during diastole and systole and wall thicknesses were measured according to the recommended criteria, and LV mass (LVMi) was calculated accordingly [187]. Echo-LVH was defined as LVMi>115 g/m^2 in men and >95 g/m^2 in women. LV and left atrial (LA) volumes were calculated by the Simpson biplane method [187] indexed to body surface area. LA enlargement (LAE) defined as LAVi≥34 ml/m^2. Mitral inflow peak early diastolic velocity (E), peak late diastolic velocity (A), E/A ratio, E wave deceleration time (DecT) were measured for diastolic function assessment[188,189]. Tissue Doppler mitral annular early diastolic velocity (e') was assessed at septal and lateral and averaged for calculation of E/e'; septal E/e'≥15, lateral E/e'≥13 and averaged ≥14 were defined as abnormal[188]. Diastolic dysfunction (DD) grade was defined as previously described as[188, 281]:

-Grade I DD: E/A <0.8, E/e'<10, pulmonary venous inflow S<D;

-Grade II DD: 0.8<E/A<1.5, E/e' > 10 or LAE, or presence of mid diastolic forward flow (L wave), or positive Valsalva (> 50% increase of E/A ratio);

- Grade III DD: E/A> 1.5, DecT<140 ms.

LV peak longitudinal strain measurements were obtained from grey scale-recorded images in the apical 4-chamber, 2-chamber and long-axis views. Strain was analysed using velocity vector imaging (Syngo VVI, Siemens Medical Solutions). GLS was measured on-line by averaging strain from the region of interest in the apical 4-chamber, 2-chamber and long-axis views. Impaired GLS was defined using cut-off of <18 %[85]. Global circumferential strain (GCS) was measured off line. Global diastolic strain was obtained by averaging all 18 segment strain values and measured according to method published by Ishii [282]. Functional capacity was assessed using a 6-min walk test distance following a standardized protocol [209].

Follow-up and primary end-point. Potential HF symptoms were assessed through regular follow-up phone calls, followed by symptom surveillance questionnaires and clinical visits. Possible heart failure signs and symptoms were reviewed by 3 independent cardiologists, and heart failure diagnosis was confirmed using the Framingham criteria for HF[110]. The primary composite end-point was defined as new-onset of HF and death of cardiovascular (CV) causes. Follow-up echocardiographic assessment of LVEF was performed to classify the patients with HF with reduced (HFrEF, LVEF<40%), mid-range (HFmrEF, LVEF 40-49%) or preserved EF [32].

Statistical analysis. Data are presented as mean (±standard deviation [SD]) after testing for normal distribution (Shapiro-Wilk test). Data deviating from normality are expressed as median (inter-quartile range [IQR]). Categorical variables are expressed as percentages. Correlation between variables was assessed with Pearson or Spearman correlation coefficients. For differences among groups, Mann-Whitney U test or t-test were used for continuous variables. Pearson's X2 tests or Fisher's Exact test were used for categorical variables. Logistic regression analysis was used to examine the association of ECG markers and abnormal echocardiographic features of SBHF. The primary outcome of time to event was examined with univariable and multivariable Cox proportional hazards models. Receiver operator characteristic analysis was used to examine the discriminative ability of variables for outcome. Comparisons of AUCs was performed with the method suggested by Hanley and McNeil. Survival analysis was performed using the Kaplan-Meier method, and the differences in survival between groups were assessed by the log-rank test. Net Reclassification Improvement (NRI) was based on quartile boundaries of probability calculated from the multivariable logistic regression for incremental value of ECG markers over clinical and echocardiographic measures for outcome. Statistical analyses were performed using a standard statistical software package (SPSS software 22.0, SPSS Inc., Chicago, IL). Statistical significance was defined by $p < 0.05$.

7.4 Results

Patient selection Baseline ECG and echocardiography were obtained in 447 individuals from the community (age 71±5 years, 47% men) who met the inclusion criteria. HF risk factors were present in all – most commonly hypertension (81%), T2DM (54%) and obesity (45%); 81% had more than one of the listed risk factors. Echocardiographic markers of SBHF were LVH (13%), DD (65% by ≥ grade 1 DD and 10% by ≥ grade 2 DD), and impaired GLS (32%). The median (IQR) for Cornell-V was 9.8 (6.8-13.6) mm; SLV 18.0 (14.1-22.7) mm, Cornell-P 1090 (786-1500) mm·ms. The mean (±SD) of minSTV5V6 was 3.1±39 and PTFV1 -2918±3532. Using the conventional cut-off values, ECG-LVH was present in 1.6% by SLV, 2% by Cornell-V and 3.1% by Cornell-P. Abnormal PTFV1 was present in 35%, abnormal minSTmV5V6 in 27% and increased heart rate in 13%.

Association of ECG markers with echocardiographic feature of SBHF. Baseline demographic, electrocardiographic and echocardiographic characteristics are listed in Table 7.38, stratified according to the presence SBHF features. Subjects with LVH and DD were older but impaired GLS was unrelated to age. However, more men had impaired GLS than women. Mean BMI was not different among groups. Hypertension and obesity were more prevalent in subjects with LVH; T2DM and obesity were more prevalent in subjects with impaired GLS. Functional capacity by 6MW was lower in those with diastolic dysfunction (DD) (p=0.02).

Using continuous measures, both Cornell-V and Cornell-P were significantly higher in groups with echocardiographic LVH (Echo-LVH), DD and impaired GLS ($p \leq 0.023$). SLV showed no differences among the groups. The overall prevalence of ECG evidence of LVH (ECG-LVH) by the listed criteria was the greatest by Cornell-P criteria - detected in 8.6% of Echo-LVH, 4.5% of DD and 6.3% of impaired GLS. By SL voltage and Cornell-V criteria, only 5.2% and 3.4% in Echo-LVH were abnormal, respectively. The 75th percentile gender specific cut-off of Cornell-P for LVH from the current cohort was 1442 mm·ms for men and 1518 mm·ms in women; this cut-off detected 45% of those with Echo-LVH, but also detected 22% of those with no Echo-LVH as being abnormal. As ECG markers are gender dependent, we further assessed their correlation with each SBHF feature stratified by gender (Table appendix 7.42). In general, correlation between men was better than women. There was significant correlation of Cornell-V and Cornell-P with LVMi, with better correlation using Cornell product than voltage. Correlation with GLS and e’ were similarly better with Cornell Product. SLV showed insignificant correlation. MinSTmV5V6 showed significant correlation with LVMi and GLS. The overall discriminative ability of 4 ECG markers for SBHF features is displayed by receiver operating characteristic (ROC) curve in Figure 7.41.

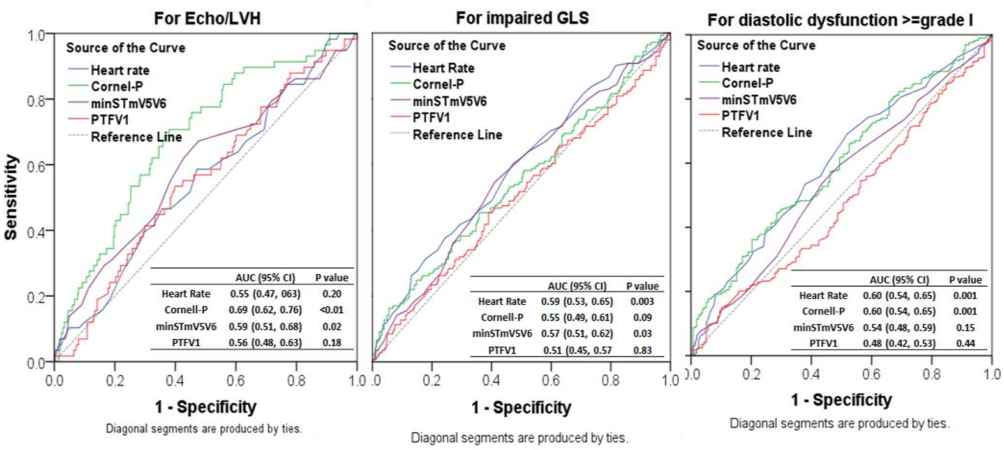
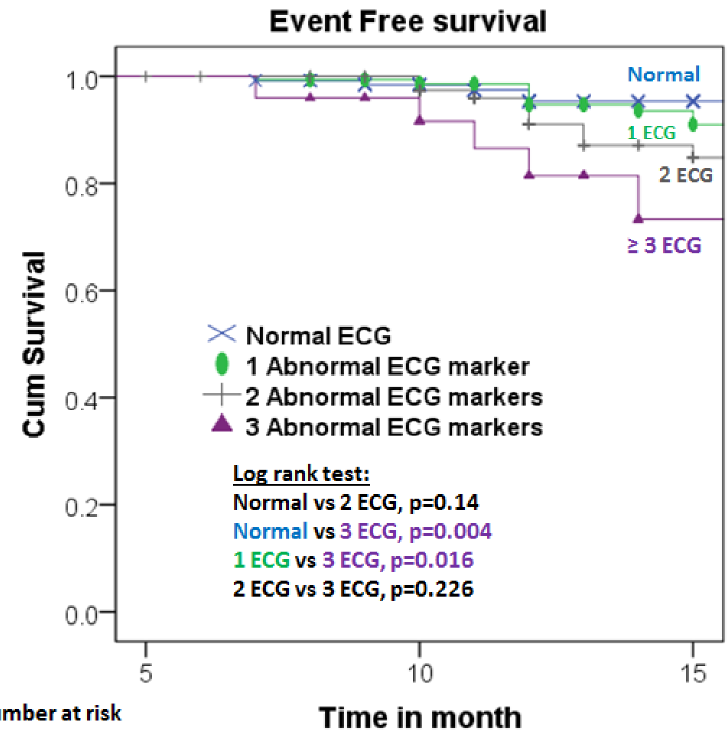


Figure 7.41 ROC analysis of ECG vs Echo features
Receiver operating characteristic (ROC) curve shows common ECG markers for discriminative characteristics for echocardiographic LVH, impaired global longitudinal strain (GLS) and for ≥ grade I diastolic dysfunction.

The independent associations of ECG markers with SBHF features are summarized in Table 7.39. Cornell-P and resting heart rate were associated with Echo-LVH, DD and impaired GLS independent of age, gender, SBP, BMI, Charlson comorbidity score and other ECG markers. One standard deviation of the mean increased Cornell-P (635 mm·ms) was associated with an odds ratio was 1.48 for Echo-LVH, 1.39 for DD and 1.37 for impaired GLS ($p<0.012$) independent of clinical variables. In multivariable analysis with all four ECG markers, the independent association of Cornell-P and increased resting heart rate remained significant, with similar effect size ($p<0.047$) (Table 7.39)**.**

Predefined cut-offs of the four abnormal ECG markers were assessed for diagnostic characteristics for echo features of SBHF. The diagnostic characteristics including sensitivity and positive predictive value (PPV) for detection of echocardiographic LVH, DD and impaired GLS are summarized in Table 7.40. Sensitivity was overall low using single marker, which improved slightly using combined markers with the expected loss of specificity from including multiple variables.

Association of ECG markers with primary outcome. After a median interval of 14±4 months, 40 individuals were lost to follow-up or alive but unable to attend follow-up. This group was no different from the remaining 407 individuals who completed follow-up (Table appendix 7.43). New HF symptoms developed in 47 patients and 4 died (2 of CV causes). The primary composite end-point of new-onset of HF and CV death occurred in 49 (12%) of the entire cohort - an annualized event-rate of 10%. Of the entire cohort, 66% had at least one abnormal ECG markers, 29% had two and 7% had all three. Figure 7.42 shows adverse outcome was proportional to the number of abnormal ECG markers.



Number at risk

Normal ECG	76	57	28
1 Abnormal ECG	213	159	87
2 Abnormal ECG	19	13	8
3 Abnormal ECG	98	72	31

Figure 7.42 Kaplan Meier plot of outcome vs abnormal ECG markers

Table 7.38 Baseline characteristics
Baseline clinical and echocardiographic characteristics stratified by LVH, diastolic dysfunction and impaired GLS.

	LVH (-) (n=389)	LVH (+) (n=58)	P value	Normal diastolic (n=158)	DD* (n=289)	P value	Normal GLS (n= 305)	Impaired GLS** (n=142)	P value
Clinical characteristics									
Age (years)	70 (67-74)	71 (68-77)	0.019	69±4	72±5	<0.001	71±5	71±5	0.787
Male, n (%)	188 (48)	20 (35)	0.049	83 (53)	125 (43)	0.060	119 (39)	89 (63)	<0.001
SBP (mmHg)	139±16	146 ±19	0.001	137±14	141±17	0.009	139±15	141±19	0.321
DBP (mmHg)	81±10	84 (±10)	0.078	80±9	82±11	0.057	80±10	84±11	<0.001
Body mass index (g/m2)	30±5	30 (±5)	0.458	29±5	30±6	0.332	29±5	30±6	0.078
Charlson Score	1.0 (0-2.0)	1.0 (0-2.0)	0.744	1 (0-2)	1 (0-2)	0.138	1.0 (0-2.0)	1.0 (0-2.0)	0.177
Type2 Diabetes, n(%)	205 (53)	36 (62)	0.182	76 (48)	165 (57)	0.068	141 (46)	100 (70)	<0.001
Obese, n(%)	167 (43)	36 (62)	0.006	66 (42)	137 (47)	0.253	125 (41)	78 (55)	0.006
Hypertension, n(%)	309 (79)	53 (91)	0.031	126 (80)	236 (82)	0.622	248 (81)	114 (80)	0.796
6-minute-walk (meter)	469±101	444 (±99)	0.066	481±98	457±100	0.019	470±96	456±108	0.171
ECG characteristics									
Heart rate (beat/min)	68±11	66±10	0.172	65±11	69±11	<0.001	67±10	70±12	0.002
QRS duration (ms)	82 (76-90)	86 (78-95)	0.047	82 (76-90)	84 (76-92)	0.489	82 (76-90)	84 (76-94)	0.147
Cornell voltage (mm)	9.5 (6.8-13.2)	11.4 (7.5-16.3)	0.006	9.1 (6.4-12.2)	10.4 (7.3-14.3)	0.015	9.1 (6.4-12.8)	11.2 (7.4-15.2)	0.001
SL voltage (mm)	18 (14-23)	18 (13-24)	0.851	18.7 (14.1-23.1)	17.7 (14.0-22.6)	0.515	17.9 (14.1-22.9)	18.2 (14.0-22.6)	0.920
Cornell product (mm·ms)	1062 (769-1440)	1431 (1093-1821)	<0.001	1020 (724-1320)	1123 (849-1558)	0.001	1079 (776-1451)	1132 (825-1637)	0.096
minSTmV5V6 (uV)	4 (-20, 29)	-10 (-40, 19)	0.021	9 (-20, 30)	0 (-24, 24)	0.166	4 (-20, 29)	-5 (-25, 19)	0.035
PTFV1 (uVms)	-3153 (-4864, -1328)	-2322 (-4193, -846)	0.189	-2844 (-4541, -1152)	-3185 (-4767, -1328)	0.479	-3139 (-4696, -1291)	-3042 (-5164, -1116)	0.738
Echo characteristics continuous									
LV mass index (BSA)	79±14	112±13	<0.001	81±17	45±11	0.044	82±16	87±19	0.004
LAVolmlm2	29±8	37 ±11	<0.001	30±8	30±9	0.808	30±9	30±9	0.901
LV ejection fraction (%)	64±6	62±7	0.035	64±5	63±6	0.079	65±5	61±7	<0.001
GLS (%)	18.6±2.5	18.0±2.7	0.103	19.0±2.4	18.3±2.6	0.004	19.9±1.6	15.6±1.6	<0.001
GCS (%)	29.4±5.6	28.9±5.1	0.466	29.6±5.6	29.2±5.5	0.404	30±5	28±6	<0.001
Mitral E/A	0.81±0.21	0.81±0.27	0.983	0.95±0.13	0.73±0.23	<0.001	0.8±0.2	0.8±0.3	0.821
DecT (ms)	249±49	258±54	0.265	231±41	261±51	<0.001	252±49	247±52	0.374
E/e' (average)	8.8±2.5	9.9±3.1	0.003	8.29±1.76	9.29±2.88	<0.001	8.9±2.6	9.1±2.5	0. 44
Diastolic Strain (%)	0.42±0.14	0.37±0.16	0.026	0.48±0.12	0.28±0.14	<0.001	0.43±2.62	0.38±0.16	<0.001
Diastolic Strain ate (1/s)	0.97±0.25	0.87±0.22	0.007	1.06±0.25	0.89±0.23	<0.001	1.02±0.2	0.82±0.2	<0.001
Echo characteristics categorical									
LV hypertrophy	-	-		15 (9.5)	43 (14.9)	0.105	35 (12)	23 (16)	0.167
Dilated LA (cut-off 34)	101 (26)	32 (55)	<0.001	42 (27)	91 (32)	0.296	90 (30)	43 (31)	0.832
Abnormal E/e' (>13)	42 (11)	12 (21)	0.031	3 (2)	51 (18)	<0.001	36 (12)	18 (13)	0.792
Abnormal GLS (<18%)	119 (31)	23 (40)	0.167	43 (27)	99 (34)	0.126	-	-	
Diastolic dysfunction>I	246 (63)	43 (74)	0.105	-	-		190 (62)	99 (70)	0.126

Data expressed as mean ±SD or median (IQR) for continuous variables. N (%) for categorical variables

*Presence of more than grade I diastolic dysfunction. ** Impaired GLS: GLS<18%. Abbreviations: DD: diastolic dysfunction; EDV: end diastolic volume; GLS: global longitudinal strain; GCS: global circumferential strain; LVH: left ventricular hypertrophy; LV: left ventricle; LA: left atrium; LVEF: LV ejection fraction; 6MW: 6-minute walk test.

Table 7.39 Association between ECG and echo markers of SBHF

	Left Ventricular hypertrophy			Diastolic dysfunction			Impaired GLS (<18%)		
	R^2	OR (95% CI)	p value	R^2	OR (95% CI)	p value	R^2	OR (95% CI)	p value
Models with each of following*									
Heart Rate (11 bpm)	0.083	0.730 (0.54, 0.99)	0.044	0.181	1.408 (1.13, 1.76)	0.003	0.136	1.538 (1.24, 1.91)	<0.001
Cornell product (635 mm·ms)	0.101	1.475 (1.14, 1.90)	0.003	0.175	1.385 (1.08, 1.78)	0.012	0.116	1.372 (1.11, 1.69)	0.003
minSTmV5V6 (39 uV)	0.080	0.747 (0.55, 1.01)	0.058	0.157	0.917 (0.74, 1.13)	0.420	0.098	0.843 (0.68, 1.04)	0.843
PTFV1 (3532 uVms)	0.075	1.239 (0.94, 1.64)	0.136	0.156	0.933 (0.75, 1.15)	0.521	0.091	0.982 (0.79, 1.21)	0.866
Model with all following									
Heart Rate (11 bpm)	0.134	0.72 (0.53, 0.99)	0.047	0.199	1.388 (1.10, 1.75)	0.005	0.158	1.522 (1.22, 1.90)	<0.001
Cornell product (635 mm·ms)		1.490 (1.13, 1.96)	0.004		1.390 (1.05, 1.84)	0.021		1.310 (1.04, 1.65)	0.021
minSTmV5V6 (39 uV)		0.869 (0.63, 1.19)	0.379		1.019 (0.81, 1.29)	0.872)		0.920 (0.73, 1.16)	0.492
PTFV1 (3532 uVms)		1.236 (0.92, 1.67)	0.166		0.979 (0.78, 1.23)	0.853		1.061 (0.85, 1.33)	0.606

* value as per standard deviation

Each model contains age, gender, heart rate, SBP, BMI, Charlson Comorbidity score; LIFE: using cut-offs from LIFE study as stated in methods

Table 7.40 Diagnostic characteristics

Diagnostic characteristics- comparison of ECG markers using conventional cut-offs, gender specific upper quartile cut-offs for detection of stage B heart failure

	Left ventricular hypertrophy			Impaired Global Longitudinal strain			Diastolic Dysfunction (≥ stage I)		
	#LVH/ total# at risk (PPV)	#LVH/total# LVH (Sensitivity)	p	#AbnGLS/ total# at risk (PPV)	#AbnGLS/total# AbnGLS (Sensitivity)	p	#DD/ total# at risk (PPV)	#DD/total# DD (Sensitivity)	p
Single ECG marker and cut-off									
Cornell Product 75th (m>1442, f>1518)	26/111 (23%)	26/58 (45%)	<0.001	42/111 (38%)	42/142 (30%)	0.113	85/111 (77%)	85/289 (29%)	0.002
Abnormal-PTFV1 (≤-4000uV·ms)	17/156 (11%)	17/58 (29%)	0.338	48/156 (31%)	48/142 (34%)	0.740	105/156 (67%)	105/289 (36%)	0.390
Abnormal-minSTmV5V6(≤-20uV)	19/119 (16%)	19/58 (32%)	0.257	45/119 (38%)	45/142 (32%)	0.098	80/119 (67%)	80/289 (28%)	0.493
Abnormal-Heart Rate(≥80bpm)	5/57 (9%)	5/58 (9%)	0.312	26/57 (46%)	26/142 (18%)	0.016	45/57 (79%)	45/289 (16%)	0.016
Combined ECG markers									
Presence of ≥ 1 abnormal ECG	44/296 (15%)	44/58 (76%)	0.096	96/296 (32%)	96/142 (68%)	0.672	205/296 (69%)	205/289 (71%)	0.004
Presence of ≥ 2 abnormal ECG	17/115 (26%)	17/58 (29%)	0.503	48/115 (42%)	48/142 (34%)	0.008	83/115 (72%)	83/289 (29%)	0.050
Presence of ≥ 3 abnormal ECG	5/29 (17%)	5/58 (9%)	0.480	15/29 (52%)	15/142 (11%)	0.017	24/29 (83%)	24/289 (8%)	0.035

PPV= positive predictive value

#=number of participants

The independent and incremental predictive value of common ECG markers for primary outcome was examined using continuous (per SD) in univariable as well as series of multivariable Cox regression models. In univariable analysis, Cornell-V (not SLV), Cornell-P, minSTmV5V6 (not PTFV1), LVMi and GLS (not DD) were significant predictors for outcome. The 75th percentile of Cornell-P showed predictive value and this association remained significant after adjusting for clinical variables (Table 7.41).

The four ECG markers (Cornell-P, minSTmV5V6, PTFV1 and heart rate) were moderately correlated (correlation coefficient: -0.01 to -0.42). When they were entered into the models together with Charlson comorbidity score, only Cornell-P showed significant association. In the subsequent analyses with echocardiographic markers, the association of either Cornell-P or minSTmV5V6 became insignificant with the presence of either LVMi or GLS (Table 7.41).

The incremental value of ECG markers over clinical measures (with and without echocardiographic features) was examined using Net Reclassification Improvement (NRI) analysis. Addition of one or two abnormal ECG to clinical information (model I), clinical + any one echo marker (model II) and any two echo markers did not demonstrate any significant incremental value for outcome with better performance of adding 2 ECG markers than 1 (NRI=-0.01 to 0.11, p>0.065) (Table appendix 7.44)
).

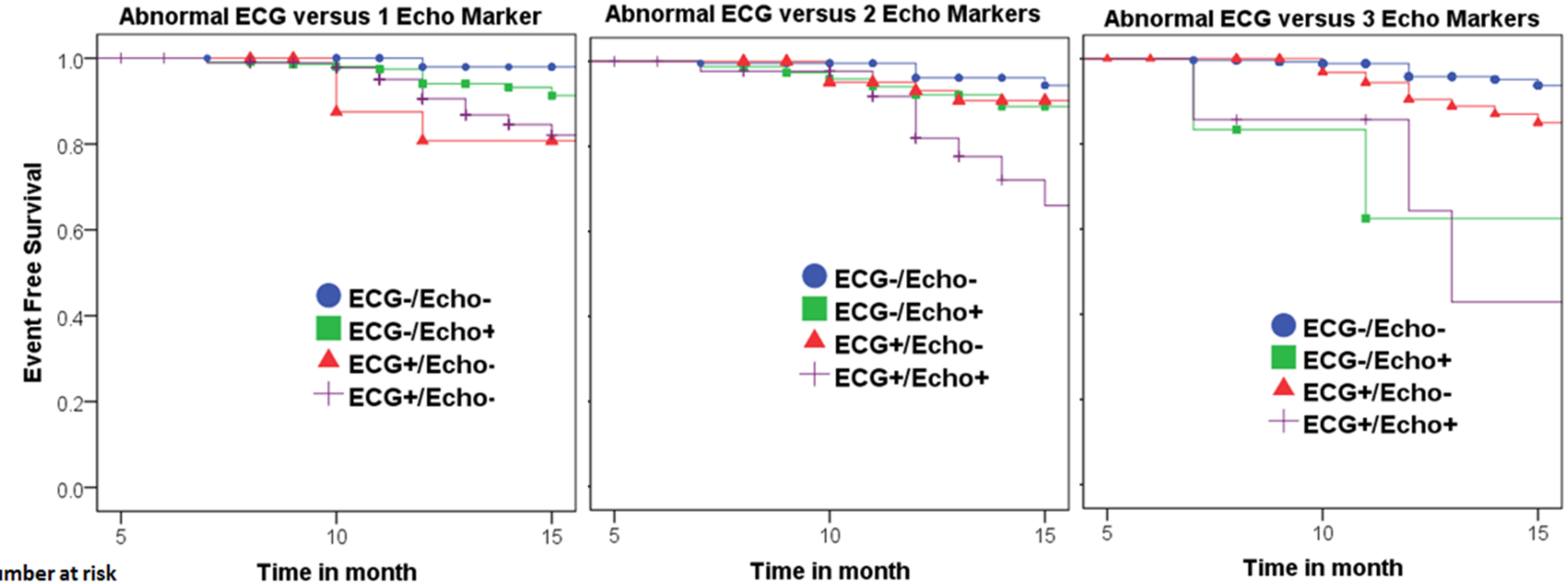
Figure 7.43 demonstrates the association of abnormal ECG (ECG+) with outcome in the presence of one (Figure 3a), two (Figure 3b) and all three (Figure 3c) abnormal echo markers. Results showed that in patients with mild cardiac abnormalities (one abnormal echo), the presence of abnormal ECG is significantly associated with outcome (Hazard ratio: 2.2, 1.04-4.68, p=0.04) regardless of echo status.

Abnormal ECG appeared to have prognostic value in those with mild disturbances of cardiac structure and function by echocardiography, although generally, more prognostic information appeared to be obtainable from echocardiography. Abnormal ECG did not add incremental value to clinical and echocardiographic assessment (Figure 7.44).

Table 7.41 Cox regression association of ECG for outcome

	Univariable Cox regression		Models I* (Clinical+ each ECG and Echo marker)			Model II**			Model III**		
Variables	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**	**C statistic**	**HR (95% CI)**	**P**	**C statistic**	**HR (95% CI)**	**P**	**C statistic**
Age (years)	1.07 (1.01, 1.13)	0.02							1.06 (0.99, 1.12)	0.07	
Male, n (%)	1.41 (0.80, 2.49)	0.23							1.41 (0.78, 2.57)	0.26	
Charlson Score	1.21 (1.10, 1.33)	<0.01				1.23 (1.12, 1.36)	<0.01				
ECG markers (per SD)											
Heart Rate (per 11 bpm)	0.81 (0.59, 1.11)	0.19	0.85 (0.61, 1.18)	0.34	0.704(0.92)	0.73 (0.53, 1.03)	0.08				
SL voltage (mm)	0.97 (0.93, 1.01)	0.13									
Cornell voltage (mm)	1.07 (1.01, 1.13)	0.02						0.701 (0.72)			0.682 (p=0.94)
Cornell product (per 635 mm·ms)	1.41 (1.10, 1.82)	0.01	1.36 (1.06, 1.76)	0.02	0.715 (0.93)	1.33 (1.01, 1.77)	0.04		1.13 (0.82, 1.54)	0.45	
minSTmV5V6 (per 39 uV)	0.69 (0.51, 0.96)	0.03	0.68 (0.49, 0.94)	0.02	0.695 (0.89)	0.78 (0.57, 1.09)	0.14		0.76 (0.55, 1.07)	0.12	
PTFV1 (per 3532 uVms)	0.97 (0.72, 1.29)	0.83	0.87 (0.64, 1.18)	0.37	0.695 (0.33)	0.92 (0.66, 1.22)	0.54				
75th Cornel-P(m≥1442;f≥1581)	1.84 (1.00, 3.85)	0.05	1.89 (1.03, 3.51)	0.04	0.704 (0.85)						
Echo markers (per SD)											
LV mass (per 17 g/m2)	1.68 (1.31, 2.16)	<0.01	1.63 (1.26, 2.12)	<0.01	0.724 (0.36)				1.48 (1.12, 1.96)	0.01	
Abnormal GLS (per 2.6%)	0.64 (0.49, 0.83)	0.001	0.74 (0.56, 0.97)	0.03	0.761 (0.03)						
Diastolic dysfunction≥ grade I	1.47 (0.76, 2.84)	0.25	1.15 (0.58, 2.28)	0.69	0.703 (0.23)						

* Model Is, each line is a model with Clinical (age, gender Charlson comorbidity Score) and each ECG and Echo marker. C-statistic for clinical=0.699
** Model II contains all 4 ECG markers: Heart rate, Cornell-P, minSTmV5V6 and PTFV1 with Charlson score;
*** Model III contains age, gender, Cornell product, minSTmV5V6 and LV mass



Number at risk	1 Echo Marker: 5	10	15	2 Echo Markers: 5	10	15	3 Echo Markers: 5	10	15
ECG-/Echo-	76	57	28	212	162	89	283	212	113
ECG-/Echo+	213	159	87	77	54	26	6	4	2
ECG+/Echo-	19	13	8	73	52	28	110	80	80
ECG+/Echo+	98	72	31	44	33	11	7	5	5

Pairwise Log rank (p value)		n	ECG (-) ECHO (-)	ECG (-) ECHO (+)	ECG (+) ECHO (-)	ECG (+) ECHO (+)	HR (95%CI)	p
ECG (-)	ECHO(-)	76	-	0.31	0.02	0.04	-	-
	ECHO(+)	213	0.31	-	0.14	0.17	1.48 (0.56, 3.87)	0.43
ECG (+)	ECHO(-)	19	0.02	0.14	-	0.77	2.21 (1.04, 4.68)	0.04
	ECHO(+)	99	0.04	0.17	0.78	-	1.37 (0.97, 1.92)	0.07

Pairwise Log rank (p value)		n	ECG (-) ECHO (-)	ECG (-) ECHO (+)	ECG (+) ECHO (-)	ECG (+) ECHO (+)	HR (95%CI)	p
ECG (-)	ECHO (-)	212	-	**0.04**	0.38	**<0.01**	-	-
	ECHO (+)	77	**0.04**	-	0.35	0.10	1.61 (0.78, 3.33)	0.19
ECG (+)	ECHO (-)	73	0.38	0.35	-	**0.02**	1.19 (0.79, 1.81)	0.40
	ECHO (+)	45	**<0.01**	0.10	**0.02**	-	1.59 (1.24, 2.04)	<0.01

Pairwise Log rank (p value)		n	ECG (-) ECHO (-)	ECG (-) ECHO (+)	ECG (+) ECHO (-)	ECG (+) ECHO (+)	HR (95%CI)	p
ECG (-)	ECHO (-)	283	-	**<0.01**	0.05	**<0.01**	-	-
	ECHO (+)	6	**<0.01**	-	**0.002**	0.56	10.7 (3.63, 31.2)	<0.01
ECG (+)	ECHO (-)	111	0.05	**0.002**	-	**<0.03**	1.21 (0.90, 1.63)	0.21
	ECHO (+)	7	**<0.01**	0.57	**<0.03**	-	1.99 (1.33, 2.97)	<0.01

Figure 7.43 Echo features of SBHF vs abnormal ECG

The presence of echo features of SBHF with/without abnormal ECG and associated outcome.

Abnormal ECG was defined as presence of any two abnormal ECG marker (Cornel-P, minSTmV5V6, PTFV1 and baseline HR). Abnormal echo was defined as the presence of any one (3a), any two (3b) or all three (3c) of LVH, impaired GLS (18% cutoff) and diastolic dysfunction.

Abnormal ECG and normal echo (ECG+/Echo-, coded red triangle) is associated with worst outcome in mild SBHF by presence of 1 echo marker.

Moderate cardiac impairment (defined by any 2 echo marker) is associated with worse outcome regardless of their ECG status.

Severe cardiac impairment (if presence of all 3 echo marker) is associated with worse outcome regardless of their ECG status

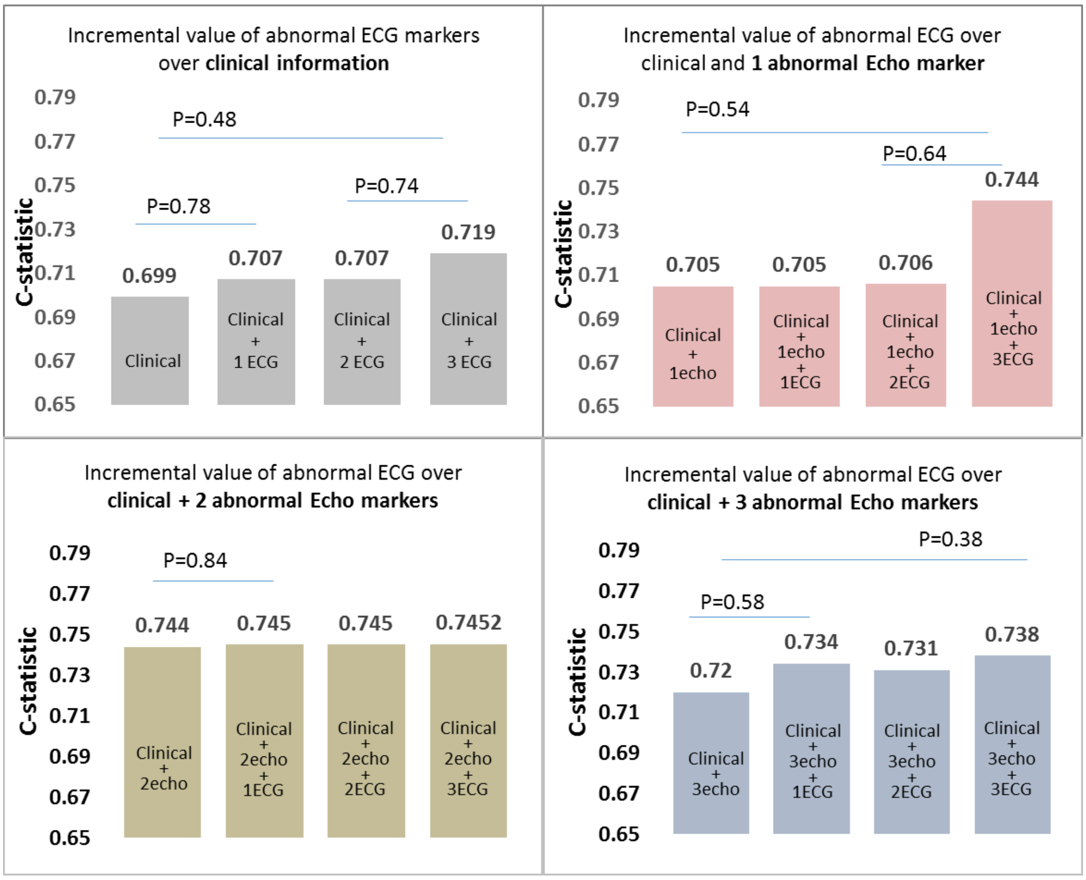


Figure 7.44 Incremental value of abnormal ECG
Incremental value of abnormal ECG over clinical and abnormal echocardiographic markers of stage B Heart Failure
Clinical was defined as age, gender and Charlson comorbidity score;
Abnormal ECG was defined as the presence of any one or more of (75th percentile of Cornell product; minSTmV5V6, PTFV1 and heart rate)
Abnormal echo was defined as the presence of any one or more of (LVH, impaired GLS and diastolic dysfunction).
Figure shows: the presence of more abnormal ECG markers had relative incremental value over clinical information only and when only one abnormal echo marker was present.

7.5 Discussion

In this heterogeneous community cohort with known non-ischemic HF risks and preserved EF, we did not find ECG markers to be of value in screening for SBHF because of low prevalence, low sensitivity, and low predictive value, compared with echocardiographic features of SBHF. However, a number of associations between ECG and new indices of LV dysfunction and outcome were identified. Cornell-P and increased resting heart rate were independently associated with echocardiographic SBHF features. Cornell-P and minSTmV5V6 were associated with primary outcome independent of clinical measures but not independent of or incremental to echocardiographic measures.

Stage B heart failure is defined as a condition with asymptomatic structural and/or functional changes in the heart. The clinical recognition of early HF can be difficult, and the prevalence of incident HF may vary broadly depending on the diagnostic criteria [345, 346]. A recent meta-analysis reported that incident HF diagnosis in 8 out of 15 included studies was based on a non-standardized clinical description[273]. Differences in the diagnostic criteria for HF may have impact on the outcome assessment in these studies. Among four commonly used HF diagnostic criteria (Framingham, Boston, Gothenburg, and European Society of Cardiology (ESC) criteria)[312], there were significant differences in predicting clinically relevant outcomes including incident hospital admission. The absolute 3-year risk of hospital admission following a Framingham HF diagnosis was 6.1% (odds ratio 2.4, 95% CI 0.8-6.8, p=0.022)[312], there were significant differences in predicting clinically relevant outcomes including incident hospital admission. The Framingham criteria seems to correlate best with echocardiography, which the gold standard to diagnose HF [312]. Accordingly, we selected the Framingham HF criteria to select subjects with HF. Echocardiography was performed in the subjects with HF to evaluate LVEF. Although we excluded any known and possible HF at baseline, the annualized rate of incident HF was 10%. A higher proportion of stage C1 at baseline may partially explain this [44]. Individuals in stage C1 had a significantly worse outcome than SBHF. A high incidence rate was observed in another community study of a cohort with combined diabetes and hypertension[57], in whom E/e' > 15 (detected in 23%) was used to categorized stage B HF. In our cohort, the prevalence of increased E/e' was lower in entire cohort (12%) but was similar in those with both HTN and T2DM (20%).

In this study, we provided a comprehensive assessment of early markers of myocardial damage (DD and strain imaging) in addition to assessment of structural cardiac changes. In the non-ischemic population with preserved LVEF, impaired GLS and diastolic dysfunction have a comparable effect on functional capacity to LVH.[70] The current guidelines have recommended that strain could be used in asymptomatic subjects at risk of HF for early detection of preclinical myocardial dysfunction [32]. Indeed, this is feasible in the community – several community-based studies have used strain, including the Northern Manhattan study [288], Framingham study [347], the CARDIA study [348], and others. Previous studies in a different population, with a significant proportion of ischemic disease have demonstrated the association of ECG changes of LVH with DD.[309] The association of ECG features of LVH with systolic function is based on LV mid-wall shortening, which is likely to be affected by LV geometry.[310] Using speckle tracking echocardiography (STE), a sensitive imaging marker for early myocardial damage, which has been linked to outcomes [65]. This study confirmed the association of ECG markers with early systolic changes by GLS, and these associations were independent of clinical measures including blood pressure, BMI and comorbidities such as diabetes and hypertension. The potential mechanisms linking abnormal ECG markers and depressed systolic function are multiple. Ischemia could be an important contributor, and is hard to exclude in a cohort with a high prevalence of hypertension and diabetes.[310] Myocardial interstitial fibrosis is another possible and important link.

Screening for SBHF in the non-ischemic population is challenging, due to a lack of feasible and effective markers. LVH is widely used as an important feature of SBHF, and can be diagnosed by ECG or echocardiography. The association of ECG-LVH with risk of incident HF has been widely recognized in a recent meta-analysis[273]. ECG-LVH and echocardiographic LVH were found to be equally predictive of incident HF in a community study after follow-up of 12 years[306]. Thus, ECG-LVH has been used as established risk component in two widely-used HF risk scores[79,80]. Other studies have proposed an independent and incremental prognostic significance of ECG-LVH over echocardiography[313,314]. However, the prevalence of ECG-LVH is known to be low, varies from 0.6-40%, with an average of 18% only if using combined multiple diagnostic criteria [315]. In the process of screening, a single ECG marker may be insufficiently effective due to its low sensitivity and positive predictive value[316]. In a community based study, Gencer studied predictive value of combined multiple ECG makers. He found combined abnormal ECG markers were present in up to 34% of population and were significantly incremental to clinical measures[305]. Given its safety, low cost and wide availability and a first-line routine examination, the ECG has an important role in the primary care. Computerized measurement facilitated a comprehensive and multi-marker approach for screening. In our study, a combination of four commonly used ECG measures had slightly improved screening sensitivity over one marker. However, its prognostic value over echo showed benefit only in those with early cardiac changes and the incremental value over echocardiogram has not been established. Thus, the relative merits of ECG or echocardiography are still controversial.

An effective screening program needs more than a feasible screening test. Screening at the primary care level faces major challenges relating to the feasibility. First, the approach to screening for SBHF is influenced by the scope of target for prevention. The intervention strategy for non-ischemic SBHF has not been well defined. It is unknown whether the presence of increased risk would justify intervention without evidence of HF. Second, traditional SBHF based on structural remodelling (LVEF and LVH) needs to be supplemented by more functional parameters,[70] which are more sensitive and can detect myocardial impairment prior to the onset of structural remodelling. Although clinical risk-based and ECG could serve to select higher risk individuals, echocardiography is still needed for guiding intervention. Third, the use of biochemical marker and hand held ultrasound devices. The sensitivity of BNP may be a particular issue in screening of non-ischemic HF, due to the effects of obesity on BNP levels.[148]. Plasma natriuretic peptides have been better markers for heart failure than they are for LV dysfunction as they reflect cardiac wall stress, which can be expected to be normal until there is an increment of filling pressure. In asymptomatic individuals, findings from studies have been heterogeneous. The sensitivity and positive predictive values of natriuretic peptides have been low – for example, the sensitivity was reported to be 30% against LVH by cardiac MRI.[317] Despite this inverse relationship, NT-proBNP was reported to provide significant prognostic information in a population study with 21 years of follow up[149]. Given the limited availability and relative cost of standard echocardiography, a hand-held ultrasound (HHU) system may able to provide a potential substitute. HHU can play an important role in structural cardiac evaluation. Although there has been growing interest in its role as a screening tool in the community, the main limitations relate to its imaging capabilities - other than assessing LVEF, the current HHU system does not provide assessment of DD or GLS.

7.6 Study Limitations

The present study was based on a community clinical trial. There are several limitations. First, because the follow-up period was short, the outcome assessment may be limited. Second, relatively high rate of incident HF in this cohort may suggest the presence of unrecognized HF at baseline. As previously reported, the possibility of high prevalence of stage C1 in this cohort may explain their rapid progress to new HF[44]. Third, the lack of protection of clinical outcome by treatment may indicate confounding by indication (i.e. the most at risk patients were treated in primary care, but were more likely to have events. Fourth, we did not obtain biomarkers (e.g.

brain natriuretic peptides), as previous work showed these were more effective in symptomatic rather than asymptomatic dysfunction.[142]. Moreover, the test performance of BNP is constrained by increasing patient age, obesity and insulin resistance.[142,148] although recently published data showed controversial results[149]. Fifth, the concomitant presence of CAD was not investigated. Atherosclerosis may co-exist with diabetic cardiomyopathy and hypertensive heart disease and may cause LV dysfunction because of CAD. We sought to exclude patients with a history consistent with CAD, but we cannot exclude an ischaemic contribution to the reported cardiac functional changes. Recruitment was partly through newspaper advertising and this may result in a population selection bias.

7.7 Conclusions

Although standard ECG markers showed low sensitivity and low positive predictive value for SBHF, Cornell-P and abnormally increased heart rate were independently associated with LVH, impaired GLS and DD. Cornell-P and ST changes showed prognostic value for clinical HF, and death of CV causes independent of clinical measures but were not incremental to echocardiography. However, ECG abnormalities were associated with poor outcome in those with early and mild echocardiographic features of impairment.

Postscript

The results of this chapter suggest that in the non-ischemic population, ECG changes were associated with cardiac remodelling, were of predictive of outcome and were not suitable for initial screening. In chapter 8, rather than being used alone, ECG is used in combination with clinical information and with functional capacity.

Next chapter will address an effective screening strategy using combined clinical risk scores, functional capacity and ECG.

Appendix tables

Table appendix 7.42 -Correlation between ECG and echo markers
Correlation between ECG markers and cardiac structural and functional measures in men and women

	LVMi		GLS		e'		E/e'		Diastolic strain		Diastolic strain rate	
	rho	P value	rho	P value	rho	P value	rho	P value	rho	P value	rho	P value
Male												
Cornell Voltage	0.394	<0.001	-0.218	0.002	-0.171	0.013	0.05	0.471	-0.197	0.004	-0.301	<0.001
SL Voltage	0.047	0.499	0.097	0.161	0.002	0.976	-0.027	0.698	0.098	0.158	0.024	0.734
Cornell product	0.403	<0.001	-0.196	0.005	-0.19	0.006	0.047	0.497	-0.196	0.005	-0.273	<0.001
minSTmV5V6	-0.301	<0.001	-0.152	0.028	0.114	0.102	-0.055	0.427	0.065	0.348	0.126	0.069
PTFV1	0.097	0.164	-0.060	0.387	-0.083	0.234	-0.011	0.870	0.054	0.438	-0.095	0.171
Female												
Cornell Voltage	0.183	0.004	-0.131	0.043	-0.249	<0.001	0.047	0.466	-0.144	0.026	-0.132	0.042
SL Voltage	0.018	0.784	0.017	0.798	0.042	0.516	0.012	0.848	0.118	0.069	0.120	0.065
Cornell product	0.263	<0.001	-0.159	0.014	-0.211	0.001	0.079	0.221	-0.109	0.092	-0.126	0.053
minSTmV5V6	-0.178	0.006	0.123	0.058	0.067	0.300	0.099	0.128	0.128	0.048	0.169	0.009
PTFV1	0.026	0.686	0.098	0.132	0.134	0.039	-0.023	0.728	0.212	0.001	0.116	0.073

GLS: global longitudinal strain; DS: diastolic strain; DSR: diastolic strain rate

Table appendix 7.43 -characteristics (completed follow-up)

	Completed follow-up (n=406)	Unable to follow-up (n=40)	p value
Age (year)	71±5	71±5	0.627
Gender male	196 (48)	12 (30)	0.028
Body Mass Index (g/m^2)	30±5	31±6	0.234
Type 2 Diabetes mellitus	218 (54)	23 (58)	0.634
Obese (BMI≥30 g/m2)	182 (45)	21 (53)	0.346
Hypertension	333 (82)	29 (73)	0.152
Previous Chemotherapy	36 (9)	5 (12)	0.445
Family history	147 (36)	13 (33)	0.649
Previous heart condition	29 (7)	6 (15)	0.077
Charlson Comorbidity score	1 (0-2)	1 (0-2)	0.595
LV Ejection fraction	64±6	64±7	0.770
GLS	18.6±2.5	18.0±2.9	0.404
Mitral E/A	0.8±0.2	0.8±0.2	0.752
Mitral e' (cm/s) (averaged)	0.08±0.02	0.08±0.02	0.399
E/e' (averaged)	8.9±2.6	9.0±2.5	0.768
Left atrium volume (ml/m2)	30±9	30±9	0.431
LV mass (g/m2)	84±18	82±16	0.521
Diastolic dysfunction	265 (65)	24 (60)	0.519
Abnormal E/e', (13)	49 (12)	5 (13)	0.932
LV hypertrophy (echo)	53 (13)	5 (13)	0.925
LA enlargement (34)	124 (31)	9 (23)	0.289
Abnormal GLS, cut-off 18	129 (32)	13 (33)	0.917
Cornell Voltage (mm)	9.9 (7.0-13.7)	8.2 (4.6-12.9)	0.115
Sokolow-Lyon L voltage (mm)	17.9 (13.9-22.9)	18.9 (14.3-22.5)	0.763
Cornell Product (mm·ms)	1093 (783-1513)	1036 (807-1409)	0.627
minSTmV5V6 (uV)	2.2±39	11.6±35	0.234
PTFV1 (uVms)	-2856±3539	-3546±3438	0.178
LV hypertrophy by SL voltage	7 (2)	0 (0)	0.403
LV hypertrophy by Cornell voltage	7 (2)	2 (5)	0.159

Continuous variable as: mean ±SD or median (IQR). Categorical variable as: n(%), GLS: global longitudinal strain; LA: left atrium; LV left ventricle

Table appendix 7.44 -Net reclassification Improvement (NRI)

Examine the incremental value of ECG over clinical (Model I), ECG marker over Clinical +1 echo (Model II) and ECG marker over Clinical +2 echo markers (Model III)

	Model I (Clinical + ≥ 2 abnormal ECG marker)					Increased Risk	Decreased Risk	Net correctly reclassified %
(Clinical)	**Composite endpoints (n=49)**	Quartile 1 (<6.24%)	Quartile 2 (6.24-9.57%)	Quartile 3 (9.57-15.6%)	Quartile 4 (≥15.69%)	n	n	%
	Quartile 1 (<6.24%)	5	0	0	0	6	1	10.2
	Quartile 2 (6.24-9.57%)	1	6	0	0			
	Quartile 3 (9.57-15.6%)	0	0	10	6			
	Quartile 4 (≥15.69%)	0	0	0	21			
						Increased Risk	Decreased Risk	Net correctly reclassified %
	No event (n=358)	Quartile 1 (<6.24%)	Quartile 2 (6.24-9.57%)	Quartile 3 (9.57-15.6%)	Quartile 4 (≥15.69%)	n	n	%
	Quartile 1 (<6.24%)	81	13	0	0	38	44	0.3
	Quartile 2 (6.24-9.57%)	16	66	14	0			
	Quartile 3 (9.57-15.6%)	0	18	61	11			
	Quartile 4 (≥15.69%)	0	0	10	67			
	Net reclassification improvement =0.11 p=0.065							0.105

Clinical=age, gender, Charlson score

	Model II (Clinical + 1 Echo +≥1 abnormal ECG)					Increased Risk	Decreased Risk	Net correctly reclassified %
(Clinical + 1Echo)	**Composite endpoints (n=49)**	Quartile 1 (<6.32%)	Quartile 2 (6.32-9.42%)	Quartile 3 (9.42-15.87%)	Quartile 4 (≥15.99%)	n	n	%
	Quartile 1 (<6.32%)	4	0	0	0	4	0	8.2
	Quartile 2 (6.32-9.42%)	3	5	0	0			
	Quartile 3 (9.42-15.87%)	0	0	11	4			
	Quartile 4 (≥15.99%)	0	0	0	22			
						Reclassified		
						Increased Risk	Decreased Risk	Net correctly reclassified %

	No event (n=358)	Quartile 1 (<6.32%)	Quartile 2 (6.32-9.42%)	Quartile 3 (9.42-15.87%)	Quartile 4 (≥15.99%)	n	n	%
	Quartile 1 (<6.32%)	83	11	0	0	37	38	0.3
	Quartile 2 (6.32-9.42%)	18	64	14	0			
	Quartile 3 (9.42-15.87%)	0	12	68	12			
	Quartile 4 (≥15.99%)	0	0	8	62			
	Net reclassification improvement (NRI)=0.085 p=0.074							0.085
	Model II (Clinical + 2 Echo +≥1 abnormal ECG)					Increased Risk	Decreased Risk	Net correctly reclassified %
(Clinical + 2 Echo)	**Composite endpoints (n=49)**	Quartile 1 (<5.69%)	Quartile 2 (5.69-9.42%)	Quartile 3 (9.42-15.76%)	Quartile 4 (≥15.76%)	n	n	%
	Quartile 1 (<5.69%)	5	0	0	0	1	4	-6.1
	Quartile 2 (5.69-9.42%)	1	5	0	0			
	Quartile 3 (9.42-15.76%)	0	1	7	1			
	Quartile 4 (≥15.76%)	0	0	2	27			
						Reclassified		
						Increased Risk	Decreased Risk	Net correctly reclassified %
	No event (n=358)	Quartile 1 (<5.69%)	Quartile 2 (5.69-9.42%)	Quartile 3 (9.42-15.76%)	Quartile 4 (≥15.76%)	n	n	%
	Quartile 1 (<5.69%)	84	11	0	0	23	40	4.7
	Quartile 2 (5.69-9.42%)	15	75	8	0			
	Quartile 3 (9.42-15.76%)	0	17	71	4			
	Quartile 4 (≥15.76%)	0	0	8	63			
	Net reclassification improvement (NRI) =-0.014							-0.014

Clinical=age, gender, Charlson score

Chapter 8

Outcome Analyses – Observational Study using Clinical Scores, ECG and Functional assessment

Article "Community Screening for Nonischemic Cardiomyopathy in Asymptomatic Subjects ≥ 65 Years with Stage B Heart Failure" was published in

American Journal of Cardiology 2016; 117 (12): 1959-65

Hong Yang, Ying Wang, Mark Nolan, Kazuaki Negishi, Peter M Okin, Thomas H Marwick

Chapter 8. Screening strategy-role of Risk scores ECG and 6MW

Community Screening for Non-Ischemic Cardiomyopathy in Asymptomatic Subjects ≥ 65 Years with Stage B Heart Failure

Introduction

The estimation of heart failure risk is a critical step in appropriate selection of patients for imaging. Findings from the systematic review (chapter 2) suggested the relative magnitude of the common non-ischemic risks, but did not provide an appropriate risk calculation algorism due to the heterogeneity of the studies. In this chapter, we aimed to apply and compare the common available risk scores of heart failure, combining ECG and baseline functional capacity. The intention was that clinical information, ECG and 6-minute walk test might be readily available in the community setting before echocardiography. If an effective screening strategy is possible, this could be used to select the highest risk individuals for echocardiography.

The following text in this chapter has been published in the ***American Journal of Cardiology 2016; 117 (12): 1959-65***

Abstract

A process to identify and target a selected population at risk of heart failure (HF) could facilitate screening and prevention. We sought to develop an effective screening process from clinical characteristics, functional capacity and electrocardiogram (ECG). Asymptomatic subjects≥65 years, with ≥1 HF risks were recruited from the community. Individuals with valvular disease, ejection fraction <40% and atrial fibrillation were excluded. All underwent clinical evaluation including assessment of HF risk using Framingham HF (FHS) and Atherosclerosis Risk in Communities (ARIC) scores, ECG, echocardiography and 6-minute walk (6MW) test. After

14±4months, new HF was assessed using Framingham criteria. A randomly selected derivation cohort was used to integrate ARIC score and 6MW in a classification and regression tree (CART) analysis, with the remaining population used for validation. Of 419 subjects (age 70±5; 48% men), 52 developed HF. ARIC was more effective than the FHS score (AUC 0.65 vs 0.53, p=0.01). CART selected ARIC (>9.5%) and 6MW (<501m) as cut-offs to define low-, intermediate- and high-risk groups. Abnormal ECG further divided the intermediate group into high and low risk. The 134 individuals identified as high risk by a combined clinical and ECG strategy showed more echocardiographic features of cardiac dysfunction including LV mass, mitral e', mitral E/e' and longitudinal strain (p<0.01). New HF was significantly more frequent than in the remaining patients (20% vs 9%, p=0.003; HR 2.08 [95% CI, 1.21-3.57], p=0.008). Thus, initial clinical risk and ECG assessment facilitate effective HF screening by identifying a high risk group.

8.1 Background

The prevalence and costs of congestive heart failure (HF) remain high and are predicted to further increase[318]. Previous randomized trials have shown that early intervention can delay or prevent the onset of overt HF in patients with reduced left ventricular ejection fraction (LVEF)[36]. However, the epidemiology of HF is changing, with increasing numbers of patients with normal LVEF. In these patients, features of stage B HF (SBHF) may be detected by left ventricular hypertrophy (LVH), abnormal diastolic function or impaired global longitudinal systolic strain (GLS)[70]. However, community-wide screening using echocardiography has not been justified[47]. An alternative would be a selective screening strategy of defining "at risk" individuals by simple clinical evaluation with subsequent echocardiography. Several community-based HF risk scores have been developed[78-80]. The Framingham HF risk (FHS) and Atherosclerosis Risk in Communities (ARIC) scores are based on clinical information that is readily available in primary care settings. Likewise, the six minute walk test (6MW) is a simple and feasible test with previous work showing improved risk assessment in SBHF[319].

8.2 Aims and Hypothesis

We hypothesized that the combination of clinical and functional variables would 1) correlate with the degree of underlying cardiac dysfunction as shown by echocardiography, and 2) predict

HF better with than without functional capacity. We sought to explore these hypotheses in a community-based study of ≥65-year-old individuals with risk factors but no symptoms of HF.

8.3 Methods

Patient selection. Participants were voluntarily enrolled through presentations to local community groups and media advertising. Data were collected prospectively from subjects ≥65 years old, living in the community, based on the presence of ≥1 HF risk factors: (1) hypertension (HTN, based on SBP >140 mmHg and self-report of HTN including anti-hypertensive medication; (2) type 2 diabetes mellitus (T2DM, based on self-report of diagnosis including medical management); (3) obesity (body mass index [BMI] ≥30); (4) previous chemotherapy; (5) family history of heart failure; and (6) previous history of heart disease (but not existing heart failure). We excluded subjects with: (1) symptoms or a known history of HF; (2) known coronary artery disease (CAD); (3) more than moderate valvular heart disease; (4) reduced LVEF (<40%) on baseline echo; (5) atrial fibrillation (AF); and (6) inability to acquire interpretable images at baseline. This study was performed in accordance with a research protocol approved by the Tasmanian Human Research Ethics Committee. Individual written informed consent was obtained from participants after explanation of the nature and purpose, complexity and level of risk of the study.

Data collection. Data were collected prospectively at facilities in the community, from all participants enrolled in the study. All underwent a physical examination and symptom questionnaire. They also underwent a standard 12 lead electrocardiogram (ECG), a comprehensive transthoracic echocardiogram and 6MW test. Blood pressure was measured twice after 10-minutes of rest in the supine position. Data were also collected on socioeconomic indicators, complete medical history, and family history of HF.

Quantification of heart failure risks. The FHS and ARIC risk scores were used to calculate the absolute risk of HF for all individuals. Calculation of FHS score (4-year probability of HF) was performed using 9 common clinical variables including age, sex, prevalence of CAD, diabetes and valve disease, LV hypertrophy (LVH) on ECG, systolic blood pressure (SBP), heart rate, and body mass index (BMI)[80]. For the ARIC score, we adopted the on-line ARIC Heart Failure Risk Calculator, which uses the 10 most common clinical variables including age, race, sex, SBP, current use of blood pressure-lowering medication, smoking status, heart rate and BMI, prevalent CAD and diabetes.[320] We made minor modifications (using open source code) to permit quantification of risk at four years.

Functional capacity. Functional capacity was measured in the community using 6MW following a standardized protocol[209]. A 25-meter flat, obstacle-free corridor was used, with visible markers at each meter interval and stop coins placed at either end. Participants were instructed to walk at the best of their effort and walked unaccompanied. Mean peak VO_2 was estimated using an established equation[210]. Age- and gender-adjusted functional capacity were estimated according to nomogram based metabolic equivalents in men[211] and women[212].

Electrocardiogram. A standard 12-lead ECG was recorded at 25 mm/s and 1 mV/cm according to standard protocol. ECG measurements were performed using MUSE software (GE Healthcare, Milwaukee, WI, USA). Cornell product (CP), defined as the product of QRS duration times Cornell voltage (R_{aVL}+S_{V3}, plus 6 mm in women), was measured in all and the reference value was derived from the 75th percentile of the study population, analogous to derivation in the LIFE study[196]. In this work, a CP >1498 mm ms was used to deemed abnormal.

Echocardiographic study. Standard transthoracic 2D and Doppler echocardiographic studies were performed using standard equipment (Siemens ACUSON SC2000, Siemens Healthcare, Mountain View, CA) and transducer (4V1c, 1.25-4.5 MHz; 4Z1c, 1.5-3.5 MHz) in accordance with the American Society of Echocardiography (ASE) guidelines[187,281]. LV dimensions during diastole and systole and wall thicknesses were measured from parasternal long-axis views according to the recommended criteria, and LV mass (LVM) was calculated accordingly[187]. LVH was defined as LVM index (LVMi) >115 g/m^2 in men and >95 g/m^2 in women. LV and left atrial (LA) volumes (LAV) were calculated by the Simpson biplane method. LAV ≥34 ml/m^2 was used as abnormal cutoff[187]. Mitral inflow peak early diastolic velocity (E), peak late diastolic velocity (A), E/A ratio, E wave deceleration time (DT) were measured for diastolic function assessment[281]. E/A ratio <0.8 was used as cut-off to designate delayed relaxation (Stage 1). Tissue Doppler mitral annular early diastolic velocity (e’) was assessed at septal and lateral and averaged for calculation of E/e’; an average E/e’≥13 was used to designate raised filling pressure[281]. LV peak longitudinal strain measurements were obtained from grey scale-recorded images in the apical 4-chamber, 2-chamber and long-axis views. Strain was analysed offline using velocity vector imaging (Syngo VVI, Siemens Medical Solutions). After manual tracing of the LV endocardial border during end-systole, this was automatically tracked throughout the cardiac cycle. LV global longitudinal strain (GLS) was obtained by averaging strain from the regional of interest in the apical 4-chamber, 2-chamber and long-axis views.

Follow-up. Potential HF symptoms were assessed through regular follow-up phone calls, followed by symptom surveillance questionnaires and clinical visits. During the process, information on all-cause hospitalization was monitored and collected. Possible heart failure signs and symptoms were reviewed by 3 independent cardiologists, and heart failure diagnosis was confirmed using the Framingham criteria for HF[110]. The primary composite endpoint was defined as new HF and cardiovascular death.

Statistical analysis. Data are presented as mean (±SD) after testing for normal distribution (Shapiro-Wilk test). Data deviating from normality are expressed as median (inter-quartile range [IQR]). Categorical variables are expressed as percentages. For differences among risk groups, the Mann-Whitney U test and the Kruskal-Wallis test were used for continuous variable and X^2 tests for categorical variables. Associations between variables were expressed with Pearson or Spearman correlation coefficients. The area under the receiver operating characteristic (ROC) curve was used to test predictive accuracy of variables, and statistical differences between the areas under the curves (AUCs) were performed with the method suggested by Hanley & McNeil[321]. Survival function was estimated by Kaplan-Meier method and the difference in survival between groups were assessed by the log-rank test.

Classification and Regression Tree (CART) analysis is a non-parametric and nonlinear method based on the repeated partitioning of a sample into subgroups by pre-defined criteria[322]. This relatively infrequently-used method provides an approach to identify at risk patients without the effects of data distribution, multi-collinearity, outliers and/or missing data, and interactions that impact other approaches[323]. The decision-tree model based on ARIC score combining 6MW distance for the prediction of new HF and cardiac death was built as follows. The main study cohort was split into a derivation (1/2) and validation cohort by random selection. The tree model was then built from the derivation cohort, whereby patients were split into binary groups with the highest contrast for outcome. In each level of the tree, the variable with the strongest relationship to the endpoint was selected and the optimal cut-off was used. The McNemar X^2 test was used to test paired data (e.g. discordance in sensitivity and specificity in dichotomous ARIC and 6MWscores). Subsequent CART validation was performed in the validation cohort, with the expectation of showing a similar proportion of correctly classified cases for each category of outcome for the derivation and validation datasets. Based on risk stratification of CART model, we further tested the discrimination ability to predict the outcome in the entire cohort. The predicted risk groups were related to echocardiographic evidence of cardiac dysfunction.

The CART model was built using commercially-available software (DTREG predictive modelling software 10.8.0, Brentwood TN, USA). Statistical analysis was performed using standard software (SPSS software 22.0, SPSS Inc., Chicago, IL) and significance was defined by $p<0.05$.

8.4 Results

Of 822 individuals from the community who were potentially eligible and volunteered for assessment, 344 were excluded due to failure to meet the clinical inclusion criteria and 42 were excluded after baseline echo screening, leaving 438 patients (median age 70 years [IQR: 67-74], 52% women) who underwent baseline testing (Figure appendix 8.49). HF risk factors were present in all – most commonly hypertension (82%), diabetes mellitus (55%) and obesity (45%); 80% had more than one of the listed risk factors. The FHS and ARIC scores were calculated in all subjects, and the median 4 year FHS and ARIC HF risks were 3.0% (IQR: 2.0-6.5%) and 5.8% (IQR: 3.4-10.4%) respectively.

After a median interval of 14±4 months, 19 of 438 participants (4%) were lost to follow-up or alive but unable to attend follow-up. This group was no different from the remaining 419 who completed follow-up (Table appendix 8.49). New HF symptoms developed in 52 patients (2 were admitted to hospital with HF) and 4 died (2 of cardiovascular causes). The primary composite end-point (events) of new-onset HF and cardiovascular death occurred in 54 (12.8%) of the entire cohort, and annualized event-rate of 11%. Participants with events were older and greater prevalence of diabetes, higher Charlson comorbidity score and total number of stage A HF risk factors ($p<0.01$). Patient report outcome measures showed the general (EurQoL-5D) and HF specific health status (Minnesota Living with HF score) were poor ($p<0.02$), Activity status (Duke Activity Score Index score) was lower ($p<0.01$).

Compared with those remaining asymptomatic, the 54 individuals who reached the composite end-point had higher ARIC score ($p<0.01$), but did not show significant differences in FHS scores ($p=0.08$). ROC analysis showed the AUC of FHS and ARIC were 0.53 (95% CI: 0.45-0.62, $p=0.415$) and 0.65 (0.57-73, $p<0.01$), respectively. The difference between AUC was 0.12 (95%CI 0.03-0.21, $p=0.01$). The discriminative ability of ARIC was significantly better than that of FHS.

Of the 419 individuals, 209 were randomly selected and defined as the derivation cohort for building the decision tree, and the rest of the cohort (n=210) was defined as validation cohort. Baseline clinical and echocardiographic characteristics of the two cohorts are shown in Table 8.45. No difference was observed in clinical and echocardiographic characteristics except for a difference in BMI. There were 25 events (12%) in the derivation cohort and 29 in the validation cohort (13%) ($p=0.57$).

The decision process was built from the derivation cohort using the ARIC score and 6MW distance. The score of importance was 100.0 for ARIC and 42.2 for 6MW. Maximum depth of the full tree was 9 and total number of group splits was 20 with 21 terminal nodes. The relative error value was 1.083 with a standard error of 0.045. From a three-level tree (Figure appendix 8.50), the best cut-point was ARIC risk of 9.5%, which corresponds to the top 29th percentile of all ARIC levels. The optimal cut-point for 6MW was 501 meters, corresponding to the lower 40th percentile of all 6MW distances.

Table 8.45 Baseline characteristics of derivation vs validation cohort

	Derivation cohort (n=209)	Validation cohort (n=210)
Age (year)	70 (67-74)	70 (67-74)
Gender male, n (%)	109 (52)	91 (43)
Body Mass Index (g/m^2)	29 (27-33)	28 (25-32)
ARIC risk score (%)	6.2 (3.6-11.2)	5.6 (3.2-9.6)
FHS risk score (%)	3.0 (2.3-5.0)	4.0 (2.0-7.0)
T2DM, n (%)	125 (59)	107 (51)
Obese, n (%)	96 (46)	94 (45)
Hypertension, n (%)	166 (79)	178 (85)
Previous Chemotherapy, n (%)	19 (9)	19 (9)
Family history, n (%)	81 (39)	73 (35)
Previous heart condition, n (%)	20 (10)	13 (6)
Charlson score	1 (0-2)	1 (0-2)
LV Ejection fraction (%)	64 (60-68)	63 (60-68)
GLS (%)	18.4 (16.9-20.3)	18.8 (16.9-20.4)
Mitral E/A	0.79 (0.67-0.92)	0.75 (0.65-0.91)
Mitral e' (cm/s) (averaged)	7.6 (6.4-8.5)	7.5 (6.4-8.9)
E/e' (averaged)	8.7 (7.2-10.5)	8.3 (6.9-10.3)
Left atrium volume (ml/m2)	30 (24-36)	29 (24-36)
LV mass (g/m2)	83 (72-97)	80 (69-94)
Abnormal E/e', cutoff 13, n (%)	28 (13)	24 (11)
LVH, n (%)	31 (15)	26 (12)
Dilated LA, n (%)	68 (33)	62 (30)
Abnormal GLS, cutoff 18, n (%)	122 (58)	131 (62)
6MW (meters)	485 (411-531)	479 (425-529)
Adjusted Functional capacity (%)	0.71 (0.62-0.80)	0.73 (0.63-0.83)

ARIC score and 6MW distance were modestly correlated (rho=0.40, p<0.01). As a categorical variable, low risk by ARIC (≤9.5) was associated with preserved exercise capacity (6MW≥ 501) in 48% and high risk (ARIC>9.5) was associated with reduced exercise capacity (6MW<501) in 78%. In the 54 patients with events, ARIC was >9.5% in 26 (48%) and 6MW was <501 meters in 43 (80%, p=0.001). However, in the 365 who remained asymptomatic, ARIC was ≤ 9.5% in 271 (74%) and 6MW was ≥501 in 159 (44%, p<0.001). The additional predictive effect of categorical 6MW to ARIC was further analysed in the entire cohort using ROC analyses. Figure 8.45 showed significant improvement with the addition of 6MW.

The combination of ARIC and 6MW defined three risk groups - low, intermediate and high – with respective event rates of 4.5%, 14% and 18%. The validation of the tree (in the validation cohort and entire cohort) is summarized in Figure 8.46.

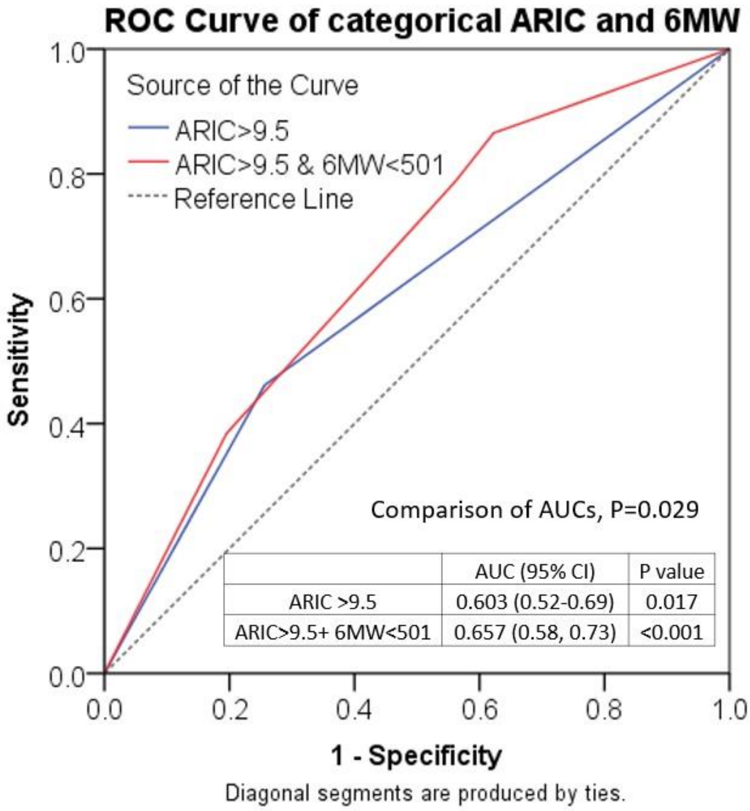


Figure 8.45 ROC of ARIC and with 6MW
Receiver operator characteristic (ROC) curves. The area under the curve is a marker of the discriminant capability of the ARIC score and its combination with 6MW.

For further analysis of appropriate combinations, tables were created by combining low and intermediate (Table 8.46a), versus combining intermediate and high risk groups (Table 8.46b). The latter showed higher sensitivity (89%), low false negative rate (11%) and high negative predictive value (96%). The exclusion of low risk subjects would allow savings in the cost of echocardiography, with a low risk of missing HF. Although restriction of screening to only high risk individuals (Table 8.46a) would limit the need for echocardiography to a smaller group (<25% of the total) but would miss more than half of the patients developing HF. The exclusion of low risk subjects and identification of high risk subjects would facilitate further screening and prevention. Individuals in intermediate risk group (n=182) were further assessed by ECG analysis using the Cornell product cut-off for separation. Of the total 182, 39 were abnormal, which were subsequently combined with CART high risk (n=95) to form a final 134 individuals as a result of screening by CART and ECG and recommended for further echocardiography.

The combination of CART and ECG strategies showed a 53% sensitivity for HF in the high risk group, and positive predictive value of 20% (Table 8.46c)**.**

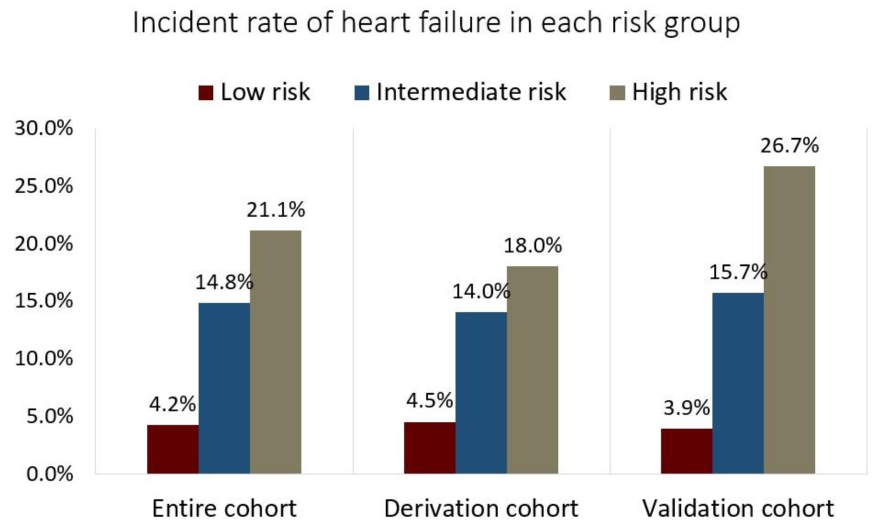


Figure 8.46 Incident rate in derivation, validation cohort entire
Low risk patients have <5% risk, intermediate risk patients have approximately 15% risk, and high risk patients have approximately 20% risk.

Table 8.46 Validation of new heart failure
Validation of new heart failure in entire cohort of three risk groups derived from CART analysis

Table 2a	Entire Cohort (n=419)		total	p=0.002
(CART only)	Heart Failure (+)	Heart Failure (-)		
High Risk	21	74	95	PPV 22%
Low & Intermediate risk	33	291	324	NPV 90%
	Sensitivity 39%	Specificity 80%		

Table 2b	Entire Cohort (n=419)			p<0.001
(CART only)	Heart Failure (+)	Heart Failure (-)		
Intermediate & High risk	48	229	277	PPV 17%
Low risk	6	136	142	NPV 96%
	Sensitivity 89%	Specificity 37%		

The definition of risks in the above table were only based on CART analysis (ARIC and 6MW)

Table 2c	Entire Cohort (n=419)		total	p=0.003
(CART+ ECG)	Heart Failure (+)	Heart Failure (-)		
High risk (CART+ ECG)	27	107	134	PPV 20%
Low risk (CART+ECG)	26	244	270	NPV 90%
	53	351		
	Sensitivity 50%	Specificity 70%		

Parameters measured by conventional and speckle tracking echocardiographic (STE) analysis were compared in two risk groups derived from the combination of clinical and ECG screening process (Table 8.47). There were significant differences in most systolic and diastolic measures**.** Individuals with high risk had significantly impaired GLS, diastolic strain and diastolic strain rate but with preserved global circumferential strain (GCS). These findings provide evidence to justify the use of echocardiography in these high risk subjects. The prevalence of SBHF features categorized by risk groups and entire cohort are shown in Figure 8.47**.** This increased risk is associated with worse outcome (Figure 8.48).

Table 8.47 Baseline characteristic in high and low risk group

Baseline Echocardiographic characteristics in high and low risk group defined by CART and ECG

	Total (n=419)	**Low risk (n=270*)**	**High risk (n=134)**	**p (MWU**)**
Age	70 (67-74)	69 (67-72)	73 (69-77)	<0.001
Gender (male %)	200 (48)	131 (49)	61 (46)	0.57
Body Mass Index	29 (26-32)	28 (26-31)	31 (27-35)	<0.001
Heart rate	67 (59-75)	65 (58-72)	71 (64-77)	<0.001
SBP	139 (128-149)	138 (127-147)	143 (132-151)	<0.001
DBP	82 (75-88)	82 (75-87)	81 (74-90)	0.916
Echo (continuous), median (IQR)				
Left ventricular volume (ml)	85 (71-103)	45 (38-51)	43 (38-53)	0.721
Relative wall thickness	0.47 (0.41-0.52)	0.46 (0.41-0.51)	0.47 (0.43-0.53)	0.029
Left ventricular mass (g/m2)	81 (71-95)	79 (69-92)	85 (75-101)	<0.001
LVEF (%)(Mean±SD)	64 (±6)	65 (±6)	62 (±7)	0.001
GLS (%)(Mean±SD	18.5 (±2.5)	18.9 (±2.3)	17.7 (±2.7)	<0.001
GCS (%)	28.9 (25-33)	29.3 (25.9-32.9)	28.5 (24.5-31.8)	0.062
E/A	0.77 (0.66-0.91)	0.80 (0.69-0.92)	0.73 (0.61-0.85)	0.001
DT (ms)	246 (219-283)	244 (219-274)	249 (218-288)	0.313
e' (cm/s) (Mean±SD)	7.6 (±1.6)	7.8 (±1.5)	7.1 (±1.64)	<0.001
E/e' averaged (Mean±SD)	8.9 (±2.6)	8.5 (±2.4)	9.8 (±2.9)	<0.001
Diastolic Strain (%)	0.42 (0.32-0.52)	0.44 (0.36-0.53)	0.36 (0.28-0.47)	<0.001
Diastolic SR (1/s)	0.93 (0.79-1.10)	0.95 (0.81-1.13)	0.85 (0.72-1.05)	<0.001
LAVI (ml/m2)	29 (24-36)	29 (24-36)	30 (25-37)	0.084
Echo (categorical), n (%)				
LV hypertrophy	57 (14)	25 (9)	30 (22)	<0.001
Abnormal GLS (cutoff 18)	165 (40)	91 (34)	65 (49)	0.004
Abnormal GLS (cutoff 16)	69 (17)	32 (12)	35 (26)	<0.001
Abnormal E/e' (13)	52 (12)	23 (9)	27 (20)	0.001
≥ Diastolic dysfunction Grade_I	273 (65)	159 (59)	104 (78)	<0.001
LA enlargement (34)	130 (31)	83 (31)	43 (32)	0.783

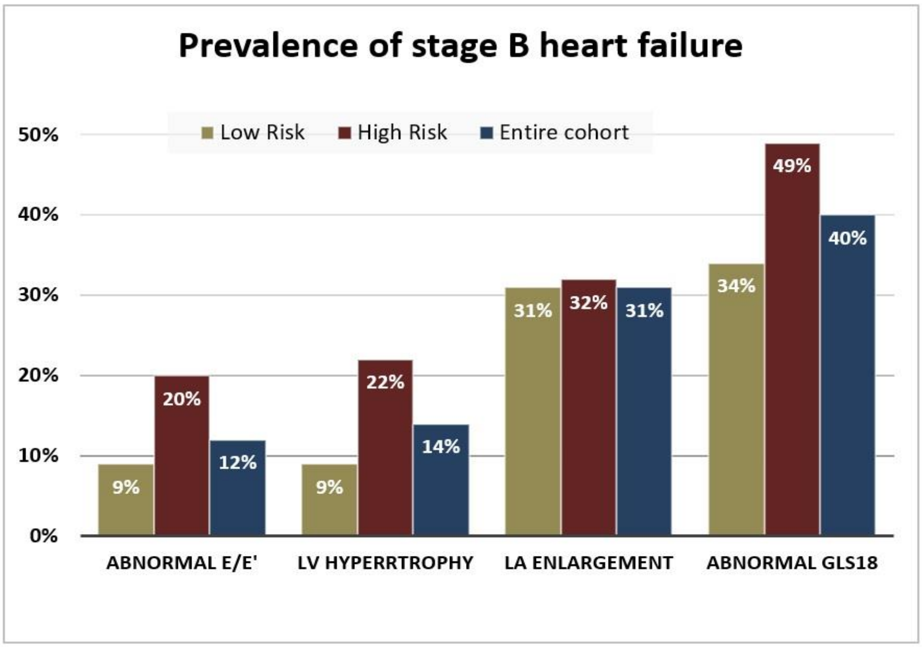


Figure 8.47 prevalence of SBHF in risk groups
Proportion of subjects with features of stage B heart failure in each risk group
Prevalence of stage B heart failure on the basis of abnormal E/e', LV hypertrophy, LA enlargement and GLS <18%. Depending on the criteria, subclinical LV disease is identified in between 9-34% of low risk patients and 12-40% of high risk patients.

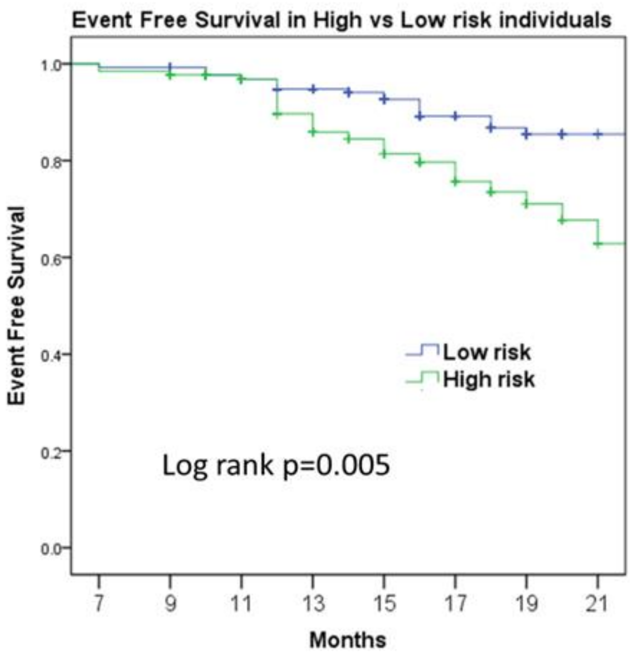


Figure 8.48 Event free survival in high versus low risk groups

8.5 Discussion

In this study, we demonstrated a risk quantification strategy using clinical characteristics and functional capacity, followed by ECG abnormalities to define low and high risk groups for new HF. The risk-level of these groups corresponds to abnormal cardiac findings and outcome at one year follow up. Findings from this study could facilitate HF screening in the community by an initial clinical and ECG screening to quantify risk, followed by echocardiography in selected (32%) high risk individuals.

Definition of new HF. Heart failure is a clinical diagnosis. Unfortunately, the clinical recognition can be difficult and the prevalence estimates vary broadly, depending on the diagnostic criteria. In a recent meta-analysis, HF diagnosis in 8 out of 15 included studies was based on a non-standardized clinical description[273]. Differences in the diagnostic criteria for HF may impact on the outcome assessment in these studies. Four commonly used HF diagnostic criteria were compared by Di Bari including Framingham, Boston, Gothenburg, and European Society of Cardiology (ESC) criteria[312]. There were significant differences between the four in predicting clinically relevant outcomes including incident hospital admission for HF. The absolute 3-year risk of hospital admission following a Framingham HF diagnosis was 6.1% and odds ratio of 2.4 (95% CI 0.8-6.8, p=0.022)[312]. Additionally, disturbances of structural and functional characteristics at baseline were best predicted using the Framingham HF criteria.[312] Accordingly, we selected the Framingham criteria for identification of new HF in our study.

Although we excluded any possible and known HF at baseline, the annualized rate of incident HF was 11%. This finding is in line with recent reports of progression of SBHF [324], and like other studies, could reflect the inclusion of stage C1 at baseline – Framingham criteria may not capture mild or early HF (stage C1) in individuals with atypical symptoms[44]. The diagnosis of this subgroup is helped by the addition of functional assessment and echocardiographic findings, and the group has a significantly worse outcome than stage B HF. A similar high incidence rate was observed in another community study of a cohort with combined diabetes and hypertension[57], in whom E/e'>15 (detected in 23%) was used to categorize stage B HF. In our study, the prevalence of increased E/e' was lower in the entire cohort (12%) but similar in the high risk group (22%). However, our findings are that abnormal GLS may be a better marker in the high and intermediate risk groups.

Heart failure prediction using risk algorithms. The optimal screening strategy to identify asymptomatic individuals at risk for incident HF is undefined. Multi-marker risk scores have been developed to facilitate the process,[78-80] but with limited external validation data, their discriminative ability for overt HF remains controversial[325]. The Framingham HF score (FHS) [80] was developed in a select population with known CAD, valvular disease and hypertension, which may explain its sub-optimal predictive performance in our study with mostly non-ischemic etiology and with insignificant valvular diseases. Although predictive power can be enhanced by the inclusion of biomarkers, this process limits the feasibility of community screening and generates additional cost.

Functional assessment is an important component to be considered in the evaluation of HF. 6MW reflects a patient's ability to perform submaximal activities and this objective measure is of prognostic value in HF [277]. Although 6MW is modestly correlated with ARIC in the prediction of HF, we anticipated that a risk stratification combining clinical characteristics and functional capacity would be valuable in the screening process. To our knowledge, our study is the first to combine 6MW into risk calculation, and may help in the selection of a subgroup for echocardiography.

Clinical implications. Risk scores for incident HF are designed to target subjects for HF prevention. The identification of low risk group (34%) suggests that further screening may not be needed in these individuals, as 96% of them will have a low probability of developing clinical HF. Their clinical management should be targeted to treating risk factors. On the other hand, the identification of high risk (23%) suggests that echocardiography is likely to show abnormal findings and these individuals are likely to benefit from cardio-protective treatment. The identification of intermediate risk accounts for nearly half of the entire population, and our findings suggest that 50% of HF comes from this group, so echocardiographic screening is recommended.

8.6 Study Limitations

The present analysis was based on a community based clinical trial and had several limitations. First, HF is a progressive disorder along the continuum of asymptomatic to symptomatic states. The possibility of high prevalence of stage C1 in this cohort (i.e. patients with mild symptoms who failed to meet Framingham HF criteria)[44], may explain their rapid progress to new HF – an observation that is in line with findings from others[44,324]. Second, we did not obtain biomarkers (e.g. brain natriuretic peptides), as previous work showed these were more effective in symptomatic rather than asymptomatic dysfunction[142]. Moreover, the test performance of BNP is constrained by increasing patient age, obesity and insulin resistance[142,148] although recently published data showed controversial results[149]. Third, findings from this study only provide a pre-screening strategy, an echocardiogram is needed for further screening. Previous evidence did not support LVEF-based community-wide screening as EF was insufficiently sensitive for detecting early myocardial disease to justify its cost[47]. However, the miniaturization and automation of echocardiography may permit new parameters to help where other failed before. Lastly, the recruitment was partly through newspaper advertising, and this may result in a population selection bias.

8.7 Conclusion

An initial quantitative clinical risk assessment of HF improves the effectiveness of screening by identifying groups at high- and intermediate-risk on clinical grounds. The sensitivity and negative predictive value of screening appear to be optimal if intermediate risk individuals are included.

Postscript

It needs to be noted that the ARIC score is a powerful risk predicting tool. In fact, we only adopted the simple online version with only 10 clinical variables, in the interest of sampling feasibility and controlling cost. The inclusion of biomarkers would improve the area under the receiving operational curve of ARIC, but its feasibility would reduce and cost would increase. Results from this study suggest a well-defined screening strategy using readily available clinical information and functional assessment. However, the presence of 40% of intermediate risk is a main concern, it means we would either screen these patients with significant additional cost or we would have missed half of the new heart failure cases within this group, were we not to screen them.

In a community cohort with multiple contributing factors, including the magnitude and duration of the primary disease and the degree of how well were treated and controlled. Selection for echocardiography continued to be challenging. No other single test is as useful as echocardiography.

The next chapter will discuss echocardiographic screening in this community cohort.

Appendix figures and tables

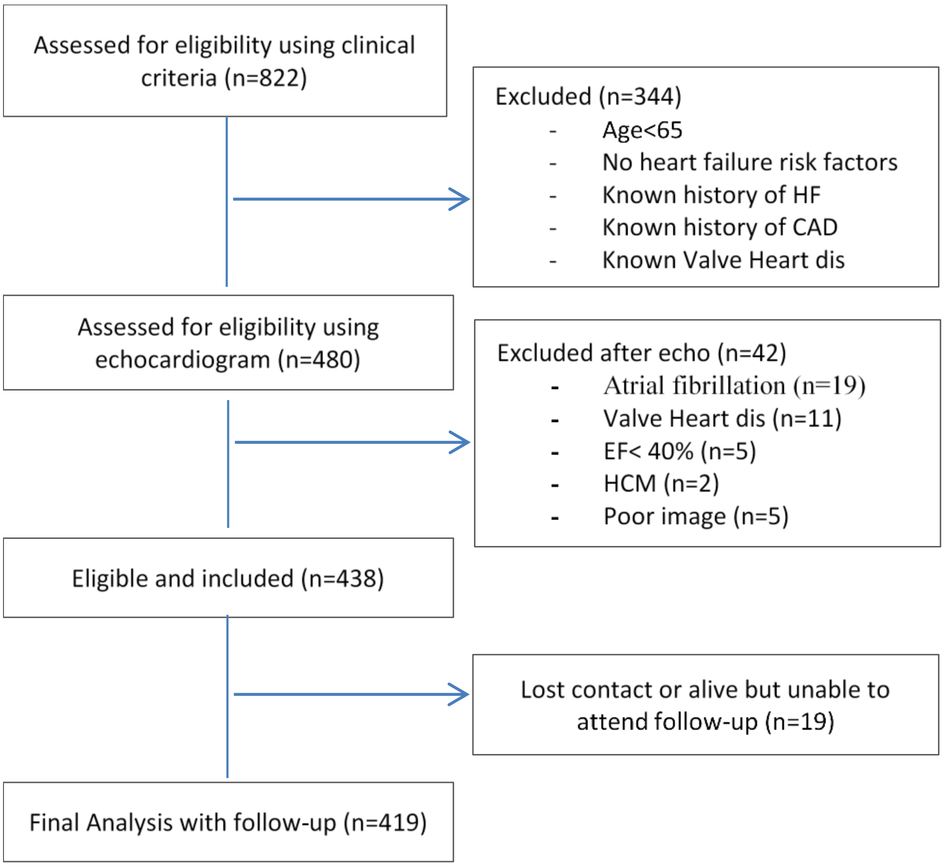


Figure appendix 8.49 -Flow chart of the recruitment of participants

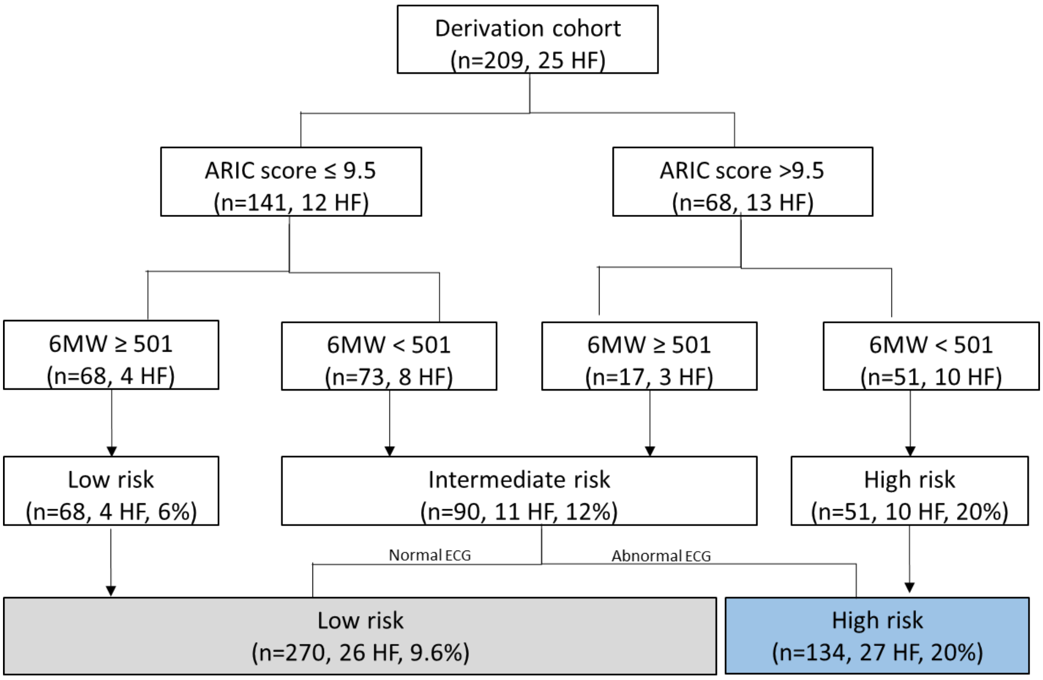


Figure appendix 8.50 -CART for new HF in derivation cohort
Classification tree for new HF based on derivation cohort discriminating low, intermediate and high risk groups

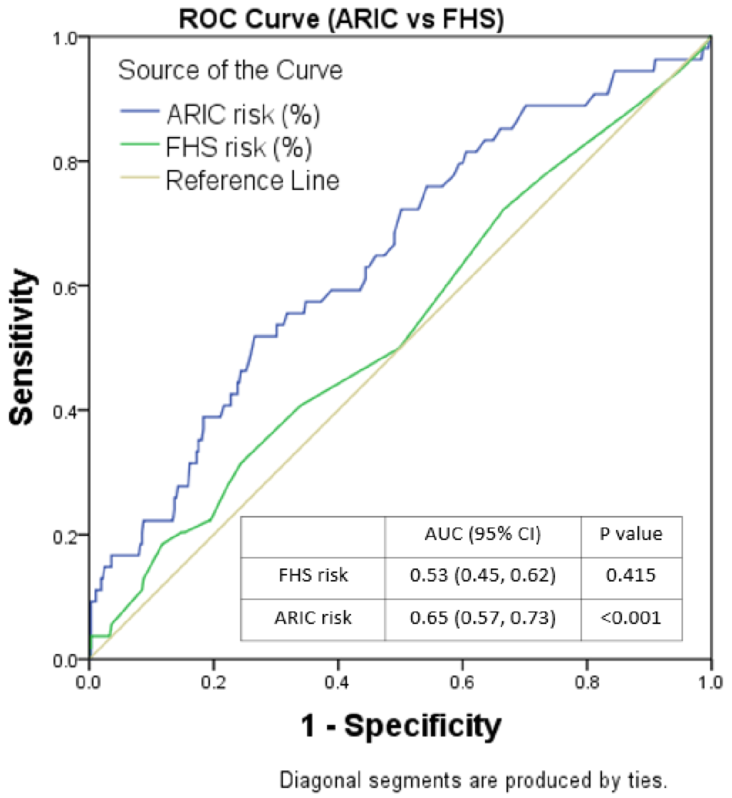


Figure appendix 8.51 -comparison of AUC of ARIC and FHS

Table appendix 8.48 -Baseline characteristics of eligible participants

	Completed follow-up (n=419)	Unable to follow-up (n=19)	P value
Age (year)	70 (67-74	69 (67-70	0.265
Gender male, n (%)	200 (47)	7 (37)	0.352
Body Mass Index (g/m^2)	29 (26-32)	28 (26-33)	0.782
ARIC risk score (%)	5.8 (3.4-10.4)	5.4 (2.8-13.7)	0.914
FHS risk score (%)	3.0 (2.0-6.5)	3.0 (3.0-6.5)	0.596
T2DM, n (%)	232 (55)	9 (47)	0.493
Obese, n (%)	190 (45)	7 (37)	0.466
Hypertension, n (%)	344 (82)	14 (74)	0.353
Previous Chemotherapy, n (%)	38 (9.1)	1 (5.3)	0.569
Family history, n (%)	154 (37)	6 (32)	0.647
Previous heart condition, n (%)	33 (8)	2 (10)	0.677
Charlson score	1 (0-2)	1 (0-3)	0.283
LV Ejection fraction (%)	64 (60-68)	64 (62-67)	0.952
GLS (%)	18.5 (16.9-20.2)	18.9 (15.1-19.6)	0.553
Mitral E/A	0.77 (0.66-0.91)	0.76 (0.64-0.96)	0.655
Mitral e' (cm/s) (averaged)	7.6 (6.4-8.7)	7.9 (7.1-9.2)	0.174
E/e' (averaged)	8.5 (7.0-10.3)	8.3 (7.6-9.0)	0.862
Left atrium volume (ml/m2)	29 (24-36)	27 (24-37)	0.46
LV mass (g/m2)	81 (71-95)	72 (70-91)	0.296
Abnormal E/e', cutoff 13, n (%)	52 (12)	2 (11)	0.807
LVH, n (%)	57 (14)	2 (11)	0.701
Dilated LA, n (%)	130 (31)	5 (26)	0.659
Abnormal GLS, cutoff 18, n (%)	166 (40)	7 (37)	0.809
6MW (meters)	482 (423-530)	462 (401-500)	0.135
Adjusted Functional capacity (%)	0.72 (0.62-0.81)	0.71 (0.56-0.81)	0.408

Chapter 9

Outcome Analyses – Best Echocardiographic Predictors for Outcome

Article "Echocardiographic Screening for Non-Ischemic Stage B Heart Failure in the Community" was published in

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Hong Yang, Kazuaki Negishi, Ying Wang, Mark Nolan, Makoto Saito, Thomas H Marwick

Chapter 9. Echocardiographic Screening – Best Echo Predictors

Introduction

The previous chapter focused on screening strategy using clinical scores and 6-minute walk test as initial steps in the screening process to select individuals at highest risk to undergo echocardiography, however, we found it possible to select out only the lowest risk patients, as the diagnoses of stage B heart failure requires echocardiography. This chapter will focus on performance of various echocardiographic markers to predict the primary outcomes in the TasELF study.

The following text in this chapter has been published in the ***European J Heart Fail. 2016; 18:1331-9.***

Abstract

Background. Incident heart failure (HF) continues to pose a common and serious problem. We sought to examine the value of echocardiographic predictors of new HF in a community-based elderly population at risk for HF, independent of and incremental to clinical evaluation.

Method. Asymptomatic patients≥65 years, with≥1 HF risk (hypertension, type 2 diabetes, obesity) were recruited from the community; patients with valve disease, reduced ejection fraction (EF) and atrial fibrillation (AF) were excluded. Patients underwent standard clinical evaluation including calculation of Charlson comorbidity score and a comprehensive echocardiography including global longitudinal strain (GLS). Functional capacity was assessed by 6 minute-walk test (6MW). New HF and cardiovascular (CV) death were assessed after a mean follow-up of 14±4 months by 3 independent cardiologists using Framingham criteria.

Results. Of 410 subjects (age 70±5 years; 48% men), the prevalence of Stage B HF was 13% (by LVH), 12% (by abnormal E/e’), 33% (by impaired GLS) and 31% (by enlarged LA, LAE). New HF symptoms developed in 49 and 2 died of CV causes, giving an event-rate of 104/1000

person-years. These patients were older (p=0.012), had higher Charlson score (p<0.001), larger LV mass and LA, higher E/e' and lower GLS (p<0.05). LAE, LVH, abnormal GLS and E/e' were independent predictors of new HF. In sequential models, LV mass and GLS added incremental information to clinical parameters. GLS significantly reclassified individuals (p=0.002), but no reclassification improvement was identified using LVMi, E/e' and LAVi.

Conclusion – Echocardiographic assessment (especially GLS and LV mass) provides incremental value in predicting incident HF.

9.1 Background

The prevalence and cost of congestive heart failure (HF) remain a common and serious problem in the community[21]. Treatment of known risk HF risk factors (stage A HF, SAHF), with more intensive targeting of its preclinical stages of asymptomatic left ventricular (LV) damage (stage B HF, SBHF) may be an effective strategy to prevent or delay the onset of HF[25]. Previous studies in ischemic SBHF patients with reduced LV ejection fraction (LVEF) have shown that early intervention can delay or prevent the onset of overt HF[34]. However, the recognition of these asymptomatic stage B patients requires imaging guidance, so choosing the right test for community screening is an important step. An ideal screening marker needs to be safe, accurate and cost-effective. Previous evidence did not support LVEF-based community-wide screening as it was insufficiently sensitive for detecting early myocardial disease to justify its cost[82]. However, recent technological developments have led to the availability of new imaging markers that are sensitive to mild LV impairment.

Among the increasing numbers of patients with non-ischemic SBHF and normal LVEF, increased LV mass[326], increased left atrial (LA) size[327], LV diastolic dysfunction and impaired global longitudinal systolic strain (GLS) [57,97]have been reported to predict new onset HF. While the extension of echocardiographic features of SBHF from reduced LVEF and/or LV hypertrophy (LVH) to impaired GLS and abnormal diastolic function has been investigated with reference to functional capacity[70], no previous comparison of these imaging markers in relation to subsequent incident HF has been reported in the literature.

9.2 Aims and Hypothesis

We aimed to compare the prediction of incident HF with common echocardiographic markers of SBHF including LV mass index (LVMi), GLS, LA volume index (LAVi) and diastolic function in a community elderly cohort with non-ischemic SAHF. We hypothesized that GLS would be the optimal screening marker for community detection of non-ischemic Stage B heart failure.

9.3 Methods

Patient selection. Participants were voluntarily enrolled through local media advertising. Data were prospectively collected from subjects ≥65 years old and living in the community. Inclusion was based on the presence of one or more of HF risk factors: 1) hypertension (HTN, based on SBP >140 mmHg and self-report of HTN including anti-hypertensive medication); 2) type 2 diabetes mellitus (T2DM, based on self-report of diagnosis including medication); 3) obesity (body mass index [BMI] ≥30); 4) previous potentially cardio toxic chemotherapy; 5) family history of heart failure; 6) previous history of heart disease (but not existing heart failure). We excluded subjects with: 1) symptoms or a known history of HF; 2) known coronary artery disease (CAD) including history of myocardial infarction, coronary artery by-pass graft and coronary stenting; 3) more than moderate valvular heart disease; 4) reduced LVEF (<40%) on baseline echo; 5) atrial fibrillation (AF); 6) inability to acquire interpretable images at baseline. This study was performed in accordance with a research protocol approved by the Human Research Ethics Committee of participating centres in Australia and New Zealand (ACTRN12614000080628). Individual written informed consent was obtained from participants after explanation of the nature and purpose, complexity and level of risk of the study.

Data collection. Data were prospectively collected at facilities in the community, from all participants enrolled in the study. All underwent a physical examination and symptom questionnaire. They also underwent a comprehensive transthoracic echocardiogram and 6MW test. Anthropometric measurements were obtained and body mass index (BMI) was calculated (body weight [kg]/height^2 [m^2]). Blood pressure was measured twice after 10-minutes of rest. Data were also collected on socioeconomic indicators, complete medical history, and family history. The Charlson comorbidity score was used for comorbidity assessment[311].

Echocardiographic study. Standard transthoracic 2D and Doppler echocardiographic studies were performed using standard equipment (Siemens ACUSON SC2000, Siemens Healthcare, Mountain View, CA) and transducer (4V1c, 1.25-4.5 MHz; 4Z1c, 1.5-3.5 MHz) in accordance with the American Society of Echocardiography (ASE) guidelines[187,281]. LV dimensions during diastole and systole and wall thicknesses were measured according to the recommended criteria, and LVMi was calculated accordingly [187]. LV hypertrophy (LVH) was defined as LVMi>115 g/m^2 in men and >95 g/m^2 in women. LV and LA volumes were calculated by the Simpson biplane method [187], and LA volume was indexed to body surface area, with LA enlargement (LAE) defined as LAVi≥34 ml/m^2.

Mitral inflow peak early diastolic velocity (E), peak late diastolic velocity (A), E/A ratio, E wave deceleration time (DecT) were measured for diastolic function assessment[281]. Tissue Doppler mitral annular early diastolic velocity (e') was assessed at septal and lateral and averaged for calculation of E/e'; an averaged E/e'≥13 was defined as abnormal[281].

LV peak longitudinal strain measurements were obtained from gray scale-recorded images in the apical 4-chamber, 2-chamber and long-axis views. Strain was analyzed using velocity vector imaging (Syngo VVI, Siemens Medical Solutions). GLS and GLS rate (GLSR) were measured on-line in the community setting by averaging strain from the regional of interest in the apical 4-chamber, 2-chamber and long-axis views. Complete analysis (in all views) was possible due to our baseline exclusion of patients with poor apical images. Impaired GLS was defined using cut-off of <18 %[85]. Global circumferential strain (GCS) and GCS rate (GCSR). Global circumferential strain (GCS) and GCS rate (GCSR) were measured off-line. Standard echocardiographic screening protocol is shown in supplementary material Table S3.

Definition of stage B heart failure. Evidence of SBHF required the presence of at least one of the following: 1) LVH; 2) LAE; 3) Abnormal E/e'; 4) Impaired GLS.

Functional capacity. Functional capacity was assessed using a 6-minute walk test (6MW) distance following a standardized protocol[209]. Mean peak VO2 was estimated using an established equation[210] for calculation of age and gender adjusted functional capacity.

Follow-up. Potential HF symptoms were assessed through regular follow-up phone calls, followed by symptom surveillance questionnaires and clinical visits. During the process, information on all-cause hospitalization was monitored and collected. Possible heart failure signs and symptoms were reviewed by 3 independent cardiologists, and heart failure diagnosis was confirmed using the Framingham criteria for HF[110]. The primary composite end-point was defined as new-onset of HF and CV death.

Statistical analysis. Data are presented as mean (±standard deviation [SD]) after testing for normal distribution (Shapiro-Wilk test). Data deviating from normality are expressed as median (inter-quartile range [IQR]). Categorical variables are expressed as percentages. For differences among groups, Mann-Whitney U test was used for continuous variables and X^2 tests for categorical variables. Associations between variables were assessed with Pearson or Spearman correlation coefficients. The primary outcome of time to event was examined with univariable and multivariable Cox proportional hazards models. The independent predictive value of continuous echo variables was assessed by adding each of LVMi, LAVi, and E/e' and GLS to an initial model based on clinical variables. The incremental value of categorical SBHF features was assessed in nested Cox models by sequential addition of LVH, LAE, abnormal E/e' and abnormal GLS. The performance of each model was compared using the Akaike's Information Criterion (AIC), and C statistic. Net Reclassification Improvement (NRI) was based on quartile boundaries of each model probability calculated from the multivariable logistic regression for incremental value of SBHF features over clinical measures[328]. Receiver operator characteristic analysis was used to examine the discriminative ability of variables for outcome. Comparisons of AUCs was performed with the method suggested by Hanley and McNeil[321].

A decision–tree model based on the four categorical SBHF markers for the prediction of events was built using classification and regression tree (CART) analysis. In each level of the tree, the variable with strongest relationship to the events was selected. The CART model was built using commercial available software (DTREG 10.8.0, Brentwood TN, USA). Other statistical analyses were performed using a standard statistical software package (SPSS software 22.0, SPSS Inc., Chicago, IL). Statistical significance was defined by $p < 0.05$.

9.4 Results

Patient selection. Of 822 individuals from the community who were potentially eligible and volunteered for assessment, 352 were excluded due to failure to meet the baseline clinical inclusion criteria and 42 were excluded after baseline echo screening, leaving 428 patients (median age 70 years [IQR:67-74], 48% men) who underwent baseline testing. HF risk factors were present in all – most commonly HTN (81%), T2DM (56%) and obesity (46%), which were present in isolation or in combination in 414 out of 428 (97%) of the entire cohort. More than one of the listed risk factors was present in 81%.

Follow-up. After a median interval of 14±4 months (492 person-years) of follow-up, 18 of 428 participants (4%) were lost to follow-up or alive but unable to attend follow-up. This group was no different from the remaining 410 individuals who completed follow-up (Table appendix 9.51). New HF symptoms developed in 49 patients, (2 were admitted to hospital with HF) and 4 died (2 of CV causes). The primary composite end-point of new-onset of HF and CV death occurred in 51 (12.4%) of the entire cohort - an event-rate of 104 per 1000 person-years.

Characteristics of individuals with and without events. Table 9.49 shows the baseline demographic, clinical characteristics of individuals with and without composite endpoint (events). Participants with events were older, had higher BMI, and greater prevalence of T2DM and higher Charlson comorbidity score. There is no difference in medication history and age and gender adjusted functional capacity.

Echocardiographic characteristics. Conventional systolic and diastolic echocardiographic characteristics are also summarized in Table 9.49. Baseline LVEF were preserved in all subjects (≥40%) and showed no differences in those with events (p=0.22). Indexed LV sizes were similar (p=0.19-0.32). Diastolic function grading according to ASE recommendation did not show difference but individuals who had events had higher prevalence of increased E/e' and LAE. Comparisons of the median of LVMi, E/e', GLS and LAVi between individuals with and without events are displayed in Figure appendix 9.56. According to conventional cut-offs of the 4 markers, the prevalence of SBHF was 13% (by LVH), 12% (by abnormal E/e'), 33% (by impaired GLS) and 31% (by LAE) in the entire population. Of the 51 individuals having events, 25 (49%) had impaired GLS, 26 (51%) had LAE, 12 (24%) had abnormal E/e' and only 10 (20%) had LVH. The annualized incident rate was 16% in LVH, 20% in abnormal E/e', 16% in impaired GLS and 17% in LAE.

Table 9.49 Baseline characteristics

Baseline clinical and echocardiographic characteristics of individuals who developed new HF or cardiovascular (CV) death

	No Event (n=359)	Event¶ (n=51)	HR (95% CI)	p value
Demographic clinical characteristics and medication history				
Age (years)	70 (67-74)	72 (68-76)	1.070 (1.02, 1.13)	0.012
Gender male (%)	167 (47)	30 (59)	1.567 (0.89, 2.74)	0.115
Body Mass Index (g/m^2)	29 (26-32)	30 (27-35)	1.080 (1.03, 1.13)	0.001
Heart rate (BPM)	67 (60-75)	65 (57-75)	0.977 (0.95, 1.01)	0.119
Systolic blood pressure (mmHg)	139 (128-149)	138 (128-147)	0.995 (0.98, 1.01)	0.526
Diastolic blood pressure (mmHg)	82 (75-87)	81 (73-87)	0.983 (0.96, 1.01)	0.202
Current smoker, n (%)	6 (2)	2 (4)	1.608 (0.39, 6.64)	0.511
Ever Smoker, n (%)	181 (50)	26 (51)	0.791 (0.45, 1.38)	0.410
Type 2 diabetes, n (%)	194 (54)	34 (67)	3.001 (1.65, 5.48)	<0.001
Obese, n (%)	156 (44)	30 (59)	2.353 (1.30, 4.25)	0.004
Hypertension, n (%)	289 (81)	46 (90)	1.450 (0.57, 3.67)	0.433
Previous Chemotherapy, n (%)	35 (10)	3 (6)	0.594 (0.18, 1.91)	0.383
Family History of cardiac disease, n (%)	137 (38)	13 (26)	0.534 (0.28, 1.00)	0.051
Past cardiac History (not HF/CAD), n (%)	18 (5)	6 (11)	1.903 (0.81, 4.49)	0.143
Total # risk factors	3 (3-4)	4 (3-4)	1.466 (1.12, 1.91)	0.005
Charlson comorbidity score	1.0 (0-2)	2.0 (1-4)	1.213 (1.11, 1.33)	<0.001
Beta blocker	21 (6)	4 (8)	1.911 (0.68, 5.34)	0.217
ACEi/ARB	242 (67)	40 (78)	1.345 (0.69, 2.63)	0.385
Diuretics	45 (14)	6 (13)	0.792 (0.33, 1.88)	0.596
Calcium Ant	72 (23)	15 (33)	1.338 (0.72, 2.49)	0.358
Lipid Lowering Meds	190 (59)	32 (69)	1.887 (1.00, 3.55)	0.049
Antiplatelet	129 (40)	19 (41)	1.159 (0.64, 2.09)	0.623
Functional Capacity				
6MW test distance	485 (427-535)	454 (387-493)	0.996 (0.99, 0.999)	0.006
Functional Capacity (adjusted)	0.72 (0.63-0.82)	0.65 (0.59-0.75)	0.980 (0.96, 1.00)	0.061
Echocardiographic continuous variables, median(IQR)				
LVEDV index (ml/m^2)	44 (38-51)	46 (38-57)	1.013 (0.99, 1.04)	0.317
LVESV index (ml/m^2)	16 (13-19)	17 (14-23)	1.034 (0.98, 1.09)	0.185
Relative Wall Thickness	0.47 (0.42-0.52)	0.47 (0.40-0.52)	2.448 (0.08, 79.4)	0.614
LV mass index (g/m2)	81 (70-95)	90 (76-105)	1.028 (1.01, 1.04)	<0.001
LVEF (%)	64 (61-68)	63 (57-67)	0.972 (0.93, 1.02)	0.220
GLS (%)	18.7 (17.1-20.4)	17.8 (15.7-19.3)	0.841 (0.76, 0.93)	0.001
GLSR (1/s)	1.3 (1.2-1.5)	1.4 (1.2-1.5)	0.746 (0.17, 3.29)	0.699
GCS (%)	28.9 (25.5-32.9)	29.1 (24.6-31.7)	0.991 (0.94, 1.05)	0.741
GCSR (1/s)	2.5 (2.1-2.9)	2.5 (2.2-2.7)	1.228 (0.83, 1.82)	0.304
Mitral E/A	0.77 (0.66-0.91)	0.75 (0.66-0.92)	0.609 (0.16, 2.39)	0.477
DecT (ms)	244 (219-276)	258 (227-306)	1.002 (0.99, 1.01)	0.464
e' (cm/s) (averaged)	7.6 (6.5-8.9)	7.1 (6.1-8.4)	0.885 (0.74, 1.06)	0.186
E/e' (averaged)	8.4 (7.0-10.3)	8.9 (6.9-11.6)	1.099 (1.00, 1.21)	0.050
Diastolic Strain (%)	0.42 (0.32-0.51)	0.42 (0.30-0.54)	0.871 (0.12, 6.16)	0.890
Diastolic Strain rate (1/s)	0.94 (0.79-1.11)	0.89 (0.71-1.02)	0.581 (0.19, 1.75)	0.335
Left atrial volume (ml/m2)	29 (24-35)	34 (26-40)	1.038 (1.01, 1.06)	0.003
Echo categorical variables, n (%)				
LV Hypertrophy (yes)	45 (13)	10 (20)	1.017 (1.01, 1.03)	0.003
Diastolic dysfunction >=grade I (yes) *	229 (64)	37 (73)	1.339 (0.72, 2.49)	0.356
Diastolic dysfunction >=grade II	36 (10)	6 (12)	1.047 (0.45, 2.46)	0.916
Abnormal E/e' (cutoff, 13) (yes)	39 (11)	12 (24)	2.236 (1.16, 4.29)	0.016
Abnormal GLS (cutoff 18) (yes)	109 (30)	25 (49)	2.204 (1.27, 3.83)	0.005
LA Enlargement (cutoff 34) (yes)	103 (29)	26 (51)	2.351 (1.35, 4.10)	0.003
Presence of any SBHF features (yes)¥	212 (59)	42 (82)	3.169 (1.54, 6.53)	0.002

¶Event=primary composite end-point (new HF and death of cardiovascular causes); *Diastolic function grading according ASE recommendation;
¥ the presence of at least one of the following: LVH, GLS<18, E/e'>13, LAE. Abbreviation: ACEi: angiotensin converting enzyme; ARB: angiotensin receptor blockers; DecT: mitral inflow deceleration time; EDV: end diastolic volume; ESV: end systolic volume; GLS: global longitudinal strain; GLSR: global longitudinal strain rate; GCS: global circumferential strain; GCSR: global circumferential strain rate; LV: left ventricle; LA: left atrium; LVEF: LV ejection fraction; 6MW: 6-minute walk test.

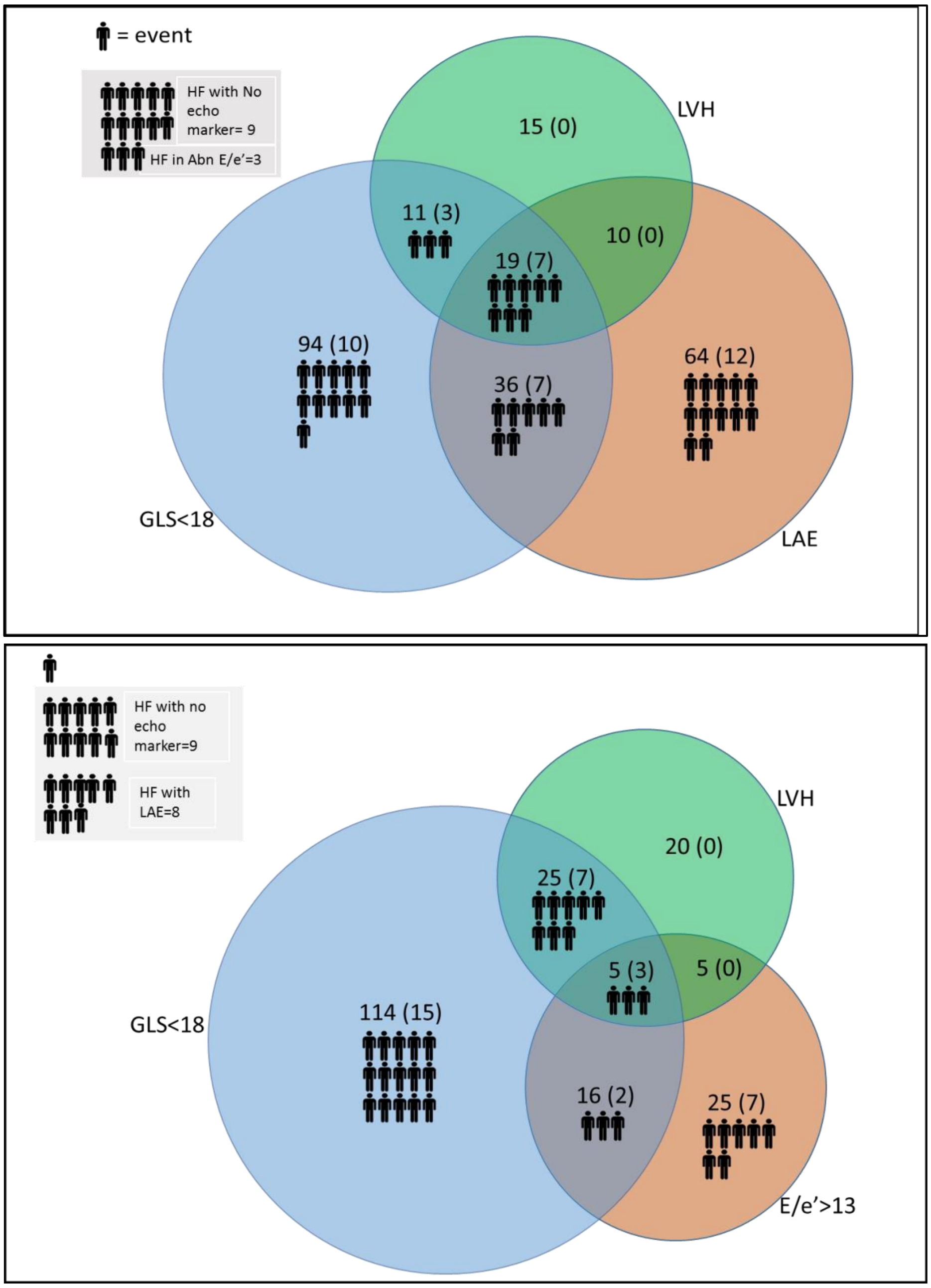


Figure 9.52 Distribution of event among SBHF features
Cases among patients with LVH, abnormal GLS, and LAE (top 1A) or abnormal E/e' (bottom 1B). Most patients with events have abnormal strain.

Of the entire cohort, 62% had ≥1 of any SBHF features. 41% had one, 15% had two, 5% had three and 1% had all four. The Hazard ratio of events was 3.17 (95% CI: 1.5-6.5, p=0.002) in those ≥1 of any SBHF features. Figure 9.52 illustrate the distribution of events according to features of SBHF**.** This level of risk increased in proportion to increasing number of SBHF features (Figure 9.53)**.**

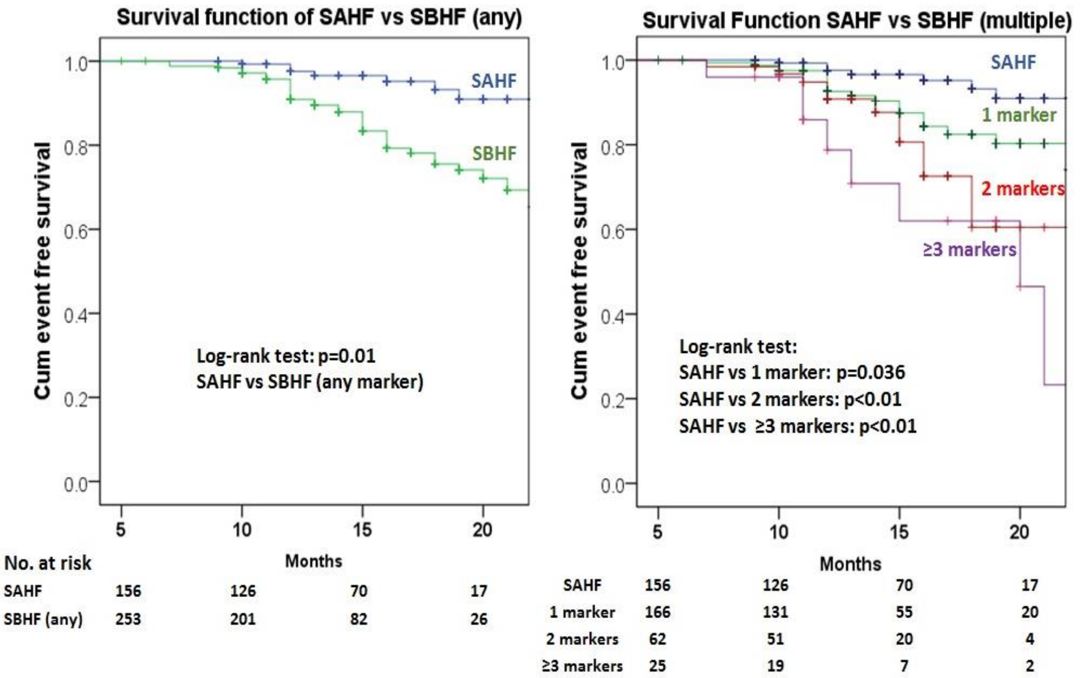
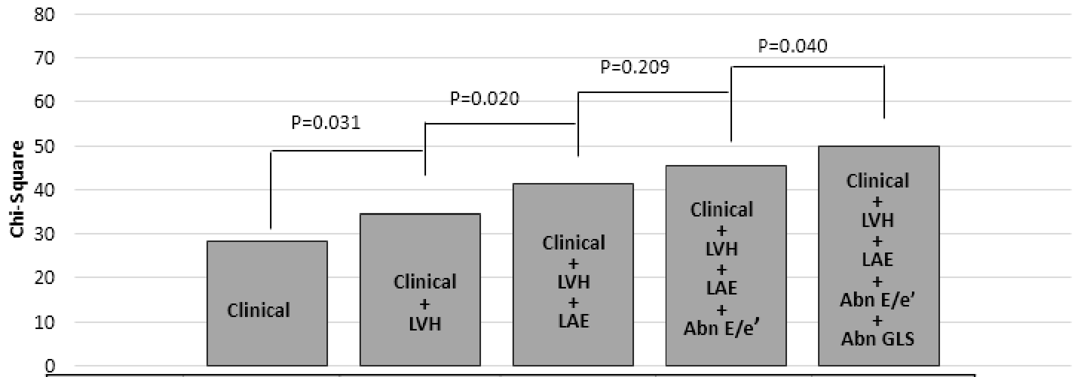


Figure 9.53 Comparison of outcome vs SBHF features
Comparison of outcomes between patients with one (left) or multiple markers of SBHF (right). There is increasing risk with increasing numbers of echocardiographic abnormalities.

Independent and incremental value of SBHF features to predict outcome. The independent and incremental predictive value of 4 SBHF markers for outcome was examined using both continuous and categorical measures using series of Cox regression models. Based on univariable analysis (Table 9.50), age, gender and Charlson comorbidity score were selected as the variables comprising the initial clinical model for subsequent analysis. In this model, age and Charlson score (but not male gender) were independent predictors. In subsequent models by adding each of the 4 SBHF markers (as continuous variables), LVMi, GLS and LAVi were predictive of outcome, independent of clinical evaluation. However, only LVMi and GLS (not LAVi and E/e') were independent predictors when all measures were combined (Table appendix 9.53)**.** Nested models were also used to assess the measures as categorical variables; LAE and impaired GLS ($p<0.038$) but not LVH and E/e' ($p>0.09$) were independent and incremental to clinical parameters (Figure 9.54)**.**



	Model I	Model II	Model III	Model IV	Model V
c statics	0.708	0.708	0.743	0.745	0.767
Chi-square	27.69	32.31 (p=0.031)	38.50 (p=0.020)	41.32 (p=0.209)	45.27 (p=0.040)
AIC	492	490	486	487	485
	HR (95%CI), p value	**HR (95%CI), p value**	**HR (95%CI), p value**	**HR (95%CI), p value**	**HR (95%CI), p value**
Age	1.067 (1.01, 1.13), 0.019	1.060 (1.01, 1.12), 0.033	1.047 (0.99, 1.11), 0.091	1.038 (0.98, 1.09), 0.189	1.031 (0.98, 1.09), 0.285
Gender	1.574 (0.89, 2.76), 0.112	1.825 (1.02, 3.27), 0.043	1.656 (0.92, 2.99), 0.095	1.574 (0.87, 2.86), 0.138	1.317 (0.71, 2.45), 0.385
Charlson	1.210 (1.11, 1.33), <0.001	1.225 (1.12, 1.34), <0.001	1.232 (1.12, 1.35), <0.001	1.230 (1.12, 1.35), <0.001	1.230 (1.12, 1.35), <0.001
LVH		2.39 (1.14, 4.99), 0.020	2.060 (0.96, 4.39), 0.060	2.020 (0.95, 4.29), 0.061	1.764 (0.81, 3.83), 0.151
LA Enlargement			2.003 (1.12, 3.58), 0.019	1.945 (1.08, 3.48), 0.026	1.942 (1.07, 3.52), 0.029
Abnormal E/e'				1.583 (0.79, 3.16), 0.194	1.806 (0.89, 3.64), 0.098
Impaired GLS					1.860 (1.03, 3.35), 0.038

Figure 9.54 Incremental value of SBHF vs clinical
Incremental value of SBHF (categorical) over clinical parameters for composite outcome. LAE and GLS showed incremental value.

Using receiver operating characteristic (ROC) analysis, the discriminatory ability of LVMi, LAVi, E/e’ and GLS without clinical variables showed AUC of LVMi, GLS and LAVi were superior to E/e’ (Figure appendix 9.57A). The discriminatory ability of clinical variables (age, gender, BMI and Charlson score) with addition of GLS (AUC: 0.72, p<0.01) exceeded that with LVMi, LAVi and E/e’ (Figure appendix 9.57B)**.** Comparison of AUC showed borderline improvement with the addition of GLS to clinical model (p=0.05), but no improvement with the addition of LVMi, LAVi and E/e’ (p>0.14). The incremental value of each SBHF feature over clinical parameters was further examined as net reclassification improvement (NRI). GLS significantly reclassified individuals into a higher risk over clinical risks (NRI: 26%, p=0.002) (Table 9.51)**,** while no NRI improvement was observed using LVMi, E/e’ and LAVi (p=0.08-0.09) (Table appendix 9.54 to 9.56)**.**

Table 9.50 Net Reclassification (Clinical characteristics +GLS)

	(Clinical + GLS)					Increased Risk	Decreased Risk	Net correctly reclassified %
	Composite endpoints (n=51)	Quartile 1 (<6.29%)	Quartile 2 (6.29-9.55%)	Quartile 3 (9.55-15.8%)	Quartile 4 (≥15.8%)	n	n	%
	Quartile 1 (<6.29%)	4	2	0	0	12	3	17.6
	Quartile 2 (6.29-9.55%)	2	1	1	1			
	Quartile 3 (9.55-15.8%)	0	0	7	8			
	Quartile 4 (≥15.8%)	0	0	1	24			
(Clinical)						Reclassified		
						Increased Risk	Decreased Risk	Net correctly reclassified %
	No event (n=359)	Quartile 1 (<6.29%)	Quartile 2 (6.29-9.55%)	Quartile 3 (9.55-15.8%)	Quartile 4 (≥15.8%)	n	n	%
	Quartile 1 (<6.29%)	85	11	1	0	51	82	8.64
	Quartile 2 (6.29-9.55%)	34	42	19	2			
	Quartile 3 (9.55-15.8%)	4	24	42	18			
	Quartile 4 (≥15.8%)	0	2	18	57			

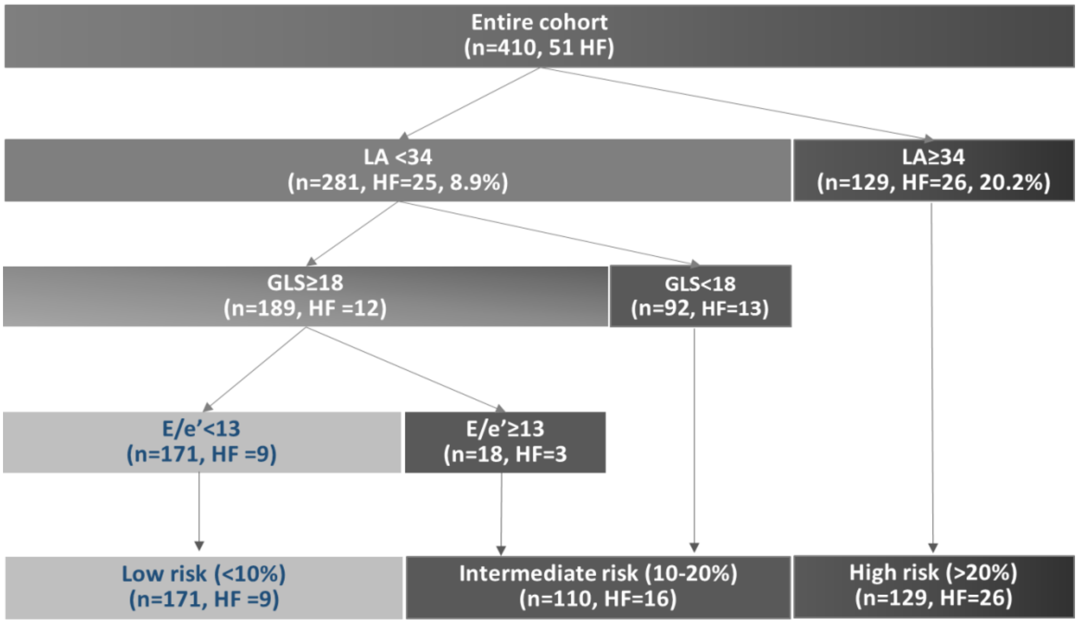


Figure 9.55 Echo screening for stage B heart failure and risk stratifications

In a decision tree based on the four SBHF markers, LAE was the strongest predictor followed by impaired GLS and abnormal E/e', defining three risk groups – low, intermediate and high-risk. This model proposed that LAE should be evaluated first, with GLS applied to patients with normal LA size, and E/e' to those with normal LA and GLS (Figure 9.55).

9.5 Discussion

The results of this study of SBHF, outcome events (mainly new HF) were associated with structural (LVH, LAE) as well as functional (GLS, E/e') changes. Of the 4 common SBHF markers, the presence of any marker is associated with a 3-folder higher risk for events. GLS and LVMi were independent predictors, but only GLS was associated with significant incremental value.

Definition of new HF. Heart failure is a clinical diagnosis. Patients in SBHF may minimize or deny their symptoms in the early phases, and clinical recognition can be difficult. The prevalence estimates may vary broadly depending on the diagnostic criteria. A recent meta-analysis reported that incident HF diagnosis in 8 out of 15 included studies was based on a non-standardized clinical description[273]. Differences in the diagnostic criteria for HF may have impact on the outcome assessment in these studies. Among four commonly used HF diagnostic criteria (Framingham, Boston, Gothenburg, and European Society of Cardiology (ESC) criteria) [312], there were significant differences in predicting clinically relevant outcomes including incident hospital admission. The absolute 3-year risk of hospital admission following a Framingham HF diagnosis was 6.1% (odds ratio 6.9, 95% CI 1.3-36.1, p=0.022) [312], and disturbances of cardiac structural and functional characteristics at baseline were best predicted using the Framingham HF criteria [312]. Accordingly, we selected the Framingham HF criteria to adjudicate events in our study. It needs to be noted, although we excluded any known and possible HF at baseline, the annualized rate of incident HF was 11%. This may partially be explained by a higher proportion of stage C1 at baseline – it is known that Framingham criteria may not capture mild or early HF (stage C1) in individuals with atypical symptoms[44], and the diagnosis of this subgroup may be helped by the addition of functional assessment and echocardiographic findings. Individuals in stage C1 had a significantly worse outcome than SBHF. A high incidence rate was observed in another community study of a cohort with combined diabetes and hypertension[57], in whom E/e' > 15 (detected in 23%) was used to categorized stage B HF. In our cohort, the prevalence of increased E/e' was lower in entire cohort (12%) but was similar in those with both HTN and T2DM (20%).

Markers of SBHF. The progression of HF is a continuum from hemodynamic disturbance to functional and structural remodeling that precede the onset of symptoms. The conventional non-valvular markers of SBHF are reduced LVEF and LVH[25], which have been found to be insensitive for early disease changes[64]; in this study, LVMi was unrelated to events (Figure 9.52)**.** Thus, not only structural markers but also systolic and diastolic dysfunction might be considered components of SBHF[70]. However, little is known about which marker(s) may symbolize the earliest changes of stage B heart failure. Ernande showed both diastolic and strain imaging are early markers[58], and these measurements are often discordant. It is unclear whether these differences reflect different disease entities of SBHF; in our study, of the 51 individuals who had events, 21 had one of four markers; 9 had impaired GLS, 3 had abnormal E/e', 9 had LAE, and none had LVH alone (Figure 9.52)**.** Markers of SBHF result from underlying causes which often co-exist, including hypertension, diabetes[286,329], obesity[330] and aging[331]; different combinations may explain some differences in their structural responses. In our analysis, GLS was consistently associated with outcome, but the CART model supports consideration of simpler measures (LAE and GLS) as the primary steps for screening, with E/e' adding most when these parameters are normal. This has improved screening efficacy by capturing majority of those with events (82%) [86].

In community screening, the balance between the prevalence of a disease and that of abnormal screening markers to be used are important determinants for screening efficacy. In a community screening study for SBHF, Mureddu used NT-proBNP and ECG screening comparing against echocardiogram as gold standard [332]. NT-proBNP screening was only sensitive in detecting those with reduced LVEF (prevalence: 1.5%), which may partially explain authors' conclusion about the inadequacy of this test in the community. The prevalence of LVEF≤50% in the local community trials was 5-6%[49], compared to 16-19% for LVH[53]; 6-7% for increased E/e'[189] and 46% for LAE (≥32 ml/m^2)[327]. The prevalence of impaired GLS in our study was 33% using a GLS cutoff of 18% and 17% with a GLS cutoff of 16%. In contrast to previous reported prevalence of 43% SBHF[44], in our study group of >65 year old subjects with HF risk factors, 62% had SBHF if any of the four markers was present, and this captured 42 out of 51 events (82%).

Clinical implications. The identification of SBHF in non-ischemic individuals is difficult, because echocardiography is not currently indicated for routine management. Clearly, an echo screening strategy is most efficient if it is restricted to a high-risk population. A previous echo screening study by Mureddu et al included 19% with known CAD and 7.4% with known valve disease; our approach to these patients have been to exclude them from screening on the basis that their disease warrants therapy. In contrast to our work, follow-up for incident HF was not defined in this study. Our findings provide evidence to justify the use of echocardiography for the prediction of adverse outcomes. Using LAE and impaired GLS, markers reflecting the burden of diastolic dysfunction and early myocardial alteration, 31% were classified as high (>20%) and intermediate risk (10-20%). In those with normal LAVi and GLS, abnormal E/e' further identified 10% of subjects who belonged to the intermediate risk group, which accounted for 46% of subjects otherwise deemed to be of low risk.

Given the recognized adverse outcome of SBHF, further effort should be made not only to identify this problem but also to monitor and potentially stop disease progression by preventive treatment. Previous trials of SBHF management were largely based on ischemic etiology with reduced LVEF[34], but effective management of non-ischemic SBHF awaits further evidence.

9.6 Study Limitations.

The present analysis was based on a community-based clinical trial and has several limitations. First, a relatively high rate of incident HF in this cohort may suggest the presence of unrecognized HF at baseline. As previously reported, the possibility of high prevalence of stage C1 in this cohort may explain their rapid progress to new HF[44]. Second, the concomitant presence of coronary artery disease (CAD) was not investigated. Diabetic cardiomyopathy and hypertensive heart disease may co-exist with atherosclerosis, which may cause LV dysfunction due to CAD. We sought to exclude patients with a history consistent with CAD, but we cannot exclude an ischemic contribution to the reported cardiac functional changes. Third, inclusion of individuals with T2DM based on self-report rather than blood results (due to feasibility and cost constraints, and may thereby underestimate the true prevalence of this disease in the community. Fourth, the lack of protection of clinical outcome by treatment may indicate confounding by indication (i.e. the most at risk patients were treated in primary care, but were more likely to have events. Fifth, we used strain rather than tissue Doppler imaging systolic component (S') for the detection of subclinical systolic dysfunction because of a desire to avoid systolic translational movement. However, it might be considered that tissue velocity is more widely available than speckle tracking. Last, recruitment from the community through self-selection inherently carries a risk of population selection bias and a relative short follow-up period is an important limitation of the current study.

9.7 Conclusion

Echocardiographic assessment provides incremental value in predicting incident HF. Impaired GLS and LVMi were independent predictors; however, impaired GLS was a more sensitive marker with significant incremental value for prediction of HF. The presence of any SBHF feature is associated with more than 3-folder higher risk.

Postscript

Findings from this chapter confirmed our hypothesis of GLS to be superior in its prognostic and incremental value over other echo markers. The uniqueness of this study was 1) a community elderly population with the mixture of multiple comorbidities. 2) GLS is compared side by side with other echo markers (LVMi, LAVi and E/e') over clinical information in this population of non-ischemic etiology. 3) In this community population, a multiple marker for diagnoses of SBHF maybe more effective, and the presence of any abnormal echo is associated with a 3-folder higher risk of new heart failure.

Although the detection of stage B heart failure is facilitated by GLS and diastology. Its value in improving outcome is predicated by treatment, which will be discussed in the next chapter.

Appendix Figures and tables

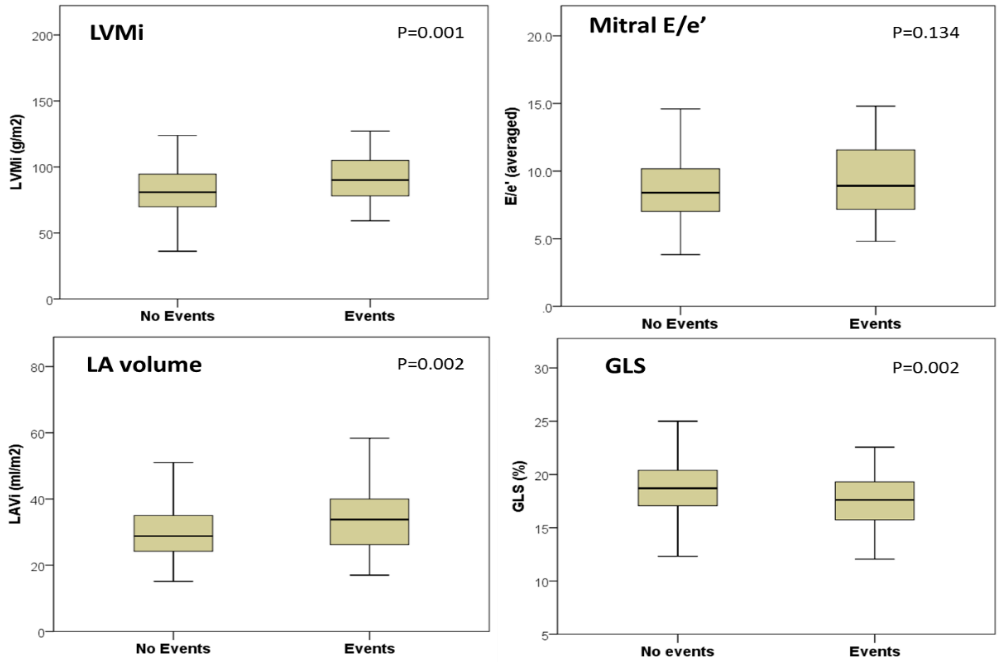


Figure appendix 9.56 -Baseline SBHF features in patients with and without HF

Comparison of baseline SBHF features in patients with and without HF. Incident HF was associated with significant differences in all markers other than E/e'.

Table appendix 9.51 -Baseline characteristics of eligible participants

	Completed follow-up (n=410)	Unable to follow-up (n=18)	p value
Age (year)	70 (67-74)	69 (67-70)	0.213
Gender male, n (%)	197 (48)	7 (39)	0.446
Body Mass Index (g/m^2)	29 (26-32)	28 (27-34)	0.616
T2DM, n (%)	228 (56)	8 (44)	0.351
Obese, n (%)	186 (45)	7 (39)	0.589
Hypertension, n (%)	335 (82)	13 (72)	0.312
Previous Chemotherapy, n (%)	38 (9)	1 (6)	0.592
Family history, n (%)	150 (37)	6 (33)	0.779
Previous heart condition, n (%)	24 (6)	1 (6)	0.958
Charlson comorbidity score	1.0 (0-2)	0.5 (0-1.5)	0.187
LV Ejection fraction (%)	64 (60-68)	63 (61-67)	0.915
GLS (%)	18.6 (16.9-20.3)	18.9 (15.1-19.7)	0.671
Mitral E/A	0.77 (0.66-0.91)	0.79 (0.67-0.98)	0.459
Mitral e' (cm/s) (averaged)	7.6 (6.4-8.7)	8.0 (7.1-9.2)	0.203
E/e' (averaged)	8.5 (7.0-10.3)	8.3 (7.6-9.2)	0.880
Left atrium volume (ml/m2)	29 (24-36)	27 (24-37)	0.622
LV mass (g/m2)	81 (71-95)	73 (69-91)	0.452
Abnormal E/e', cut-off 13, n (%)	51 (12)	2 (11)	0.867
LV Hypertrophy, n (%)	55 (13)	2 (11)	0.778
LA Enlargement, n (%)	129 (32)	5 (28)	0.736
Abnormal GLS, cu-toff 18, n (%)	126 (31)	5 (28)	0.790
Adjusted Functional capacity (%)	0.71 (0.62-0.81)	0.67 (0.56-0.79)	0.235

GLS: global longitudinal strain; LA: left atrium; LV: left ventricle; T2DM: type 2 diabetes mellitus

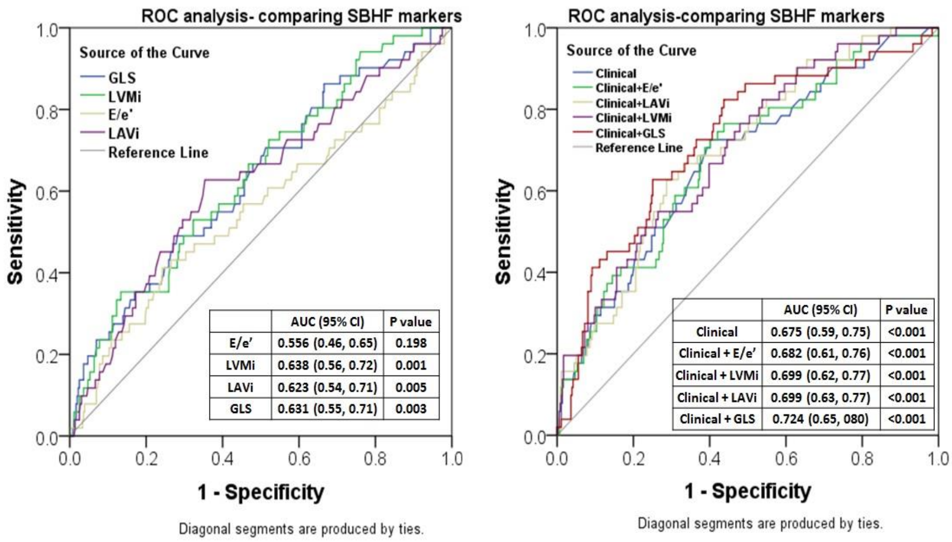


Figure appendix 9.57 -ROC Analysis SBHF vs clinical information

Receiver operating characteristic curves for events, discriminatory ability of each of GLS, LVMi, LAVi, E/e' (A) and in combination (B)

Clinical variable: age, gender, BMI, charlson;

LVMi: left ventricular mass index; LAVi: left atrial volume index; GLS: global longitudinal strain.

Table appendix 9.52 -Nested sequential model

Independent associations of SBHF features with new heart failure and Cox regression models (clinical, clinical + each and combined SBHF markers)

	Model I (Clinical)		Model II (Clinical + LVMi)		Model III (Clinical +LAVi)		Model IV (Clinical +E/e')		Model V (Clinical+ GLS)		Model VI (all)	
Chi-square	27.69		39.95		34.43		30.75		31.91		44.38	
c statics	0.708		0.73		0.742		0.725		0.767		0.771	
AIC	492		482		489		452		490		480	
	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p
Age	1.067 (1.01, 1.13)	0.019	1.054 (1.00, 1.11)	0.05	1.051 (0.99, 1.11)	0.071	1.056 (0.99, 1.12)	0.059	1.063 (1.01, 1.12)	0.029	1.036 (0.98, 1.09)	0.231
Gender	1.574 (0.89, 2.76)	0.112	1.284 (0.73, 2.27)	0.391	1.499 (0.86, 2.62)	0.157	1.612 (0.92, 2.82)	0.095	1.296 (0.72, 2.33)	0.387	1.142 (0.63, 2.06)	0.659
Charlson	1.210 (1.11, 1.33)	<0.001	1.223 (1.11, 1.34)	<0.001	1.213 (1.11, 1.33)	<0.001	1.208 (1.10, 1.32)	<0.001	1.191 (1.08, 1.31)	<0.001	1.210 (1.10, 1.33)	<0.001
LVMi			1.027 (1.01, 1.04)	<0.001							1.021 (1.00, 1.04)	0.019
LAVi					1.033 (1.01, 1.06)	0.015					1.010 (0.98, 1.04)	0.533
E/e'							1.084 (0.98, 1.19)	0.117			1.056 (0.96, 1.17)	0.289
GLS									0.884 (0.79, 0.99)	0.028	0.877 (0.78, 0.99)	0.027

Clinical model: age, gender and Charlson comorbidity score

AIC: Akaike information criterion; E/e' mitral early diastolic peak velocity/mitral annular tissue velocity; GLS: global longitudinal strain; HR: hazard ratio; LAVi: left atrial volume index; LVMi: left ventricular mass index.

Table appendix 9.53 -Net Reclassification (Clinical characteristics +LVMi)

		(Clinical + LVMi)				Increased Risk	Decreased Risk	Net correctly reclassified %
(Clinical)	**Composite endpoints (n=51)**	Quartile 1 (<5.38%)	Quartile 2 (5.39-9.49%)	Quartile 3 (9.49-16.01%)	Quartile 4 (≥16.01%)	n	n	%
	Quartile 1 (<5.38%)	2	1	1	0			
	Quartile 2 (5.39-9.49%)	1	5	1	0	8	6	3.92
	Quartile 3 (9.49-16.01%)	0	4	6	5			
	Quartile 4 (≥16.01%)	0	0	1	24			
						Reclassified		
						Increased risk	Decreased Risk	Net correctly reclassified %
	No event (n=359)	Quartile 1 (<5.38%)	Quartile 2 (5.39-9.49%)	Quartile 3 (9.49-16.01%)	Quartile 4 (≥16.01%)	n	n	%
	Quartile 1 (<5.38%)	60	12		0			
	Quartile 2 (5.39-9.49%)	40	59	21	3	51	82	8.64
	Quartile 3 (9.49-16.01%)	1	21	54	15			
	Quartile 4 (≥16.01%)	0	1	19	55			
	Net reclassification improvement (NRI)							12.56
	p=0.1141							

Clinical= age, gender, Charlson and BMI

Table appendix 9.54 -Net Reclassification (Clinical characteristics +LAVi)

		Reclassified						
		(Clinical + LAVi)				Increased Risk	Decreased Risk	Net correctly reclassified %
(Clinical) Age, gender, BMI, Charlson	**Composite endpoints (n=54)**	Quartile 1 (<7.39%)	Quartile 2 (7.39-11.04%)	Quartile 3 (11.04-17.04%	Quartile 4 (≥17.05%)	n	n	%
	Quartile 1 (<7.39%)	3	2	1	0	7	10	-5.56
	Quartile 2 (7.39-11.04%)	1	3	3	0			
	Quartile 3 (11.04-17.04%	0	4	12	1			
	Quartile 4 (≥17.05%)	0	0	5	19			
						Increased Risk	Decreased Risk	Net correctly reclassified %
	No event (n=365)	Quartile 1 (<7.39%)	Quartile 2 (7.39-11.04%)	Quartile 3 (11.04-17.04%	Quartile 4 (≥17.05%)	n	n	%
	Quartile 1 (<7.39%)	87	12	0	0	43	75	8.77
	Quartile 2 (7.39-11.04%)	28	53	12	3			
	Quartile 3 (11.04-17.04%	0	19	54	16			
	Quartile 4 (≥17.05%)	0	1	27	53			
NRI=0.0321 P=0.6951								0.0321

Clinical= age, gender, Charlson and BMI

Table appendix 9.55 -Net Reclassification (Clinical characteristics +E/e')

	(Clinical + E/e')					Reclassified Increased Risk	Reclassified Decreased Risk	Net correctly reclassified %
(Clinical) Age, gender, BMI, Charlson	**Composite endpoints (n=54)**	Quartile 1 (<7.39%)	Quartile 2 (7.39-11.04%)	Quartile 3 (11.04-17.04%	Quartile 4 (≥17.05%)	n	n	%
	Quartile 1 (<7.39%)	6	0	0	0	5	8	-5.56
	Quartile 2 (7.39-11.04%)	1	5	1	0			
	Quartile 3 (11.04-17.04%	0	2	11	4			
	Quartile 4 (≥17.05%)	0	0	5	19			
						Increased Risk	Decreased Risk	Net correctly reclassified %
	No event (n=365)	Quartile 1 (<7.39%)	Quartile 2 (7.39-11.04%)	Quartile 3 (11.04-17.04%	Quartile 4 (≥17.05%)	n	n	%
	Quartile 1 (<7.39%)	90	9	0	0	26	51	6.85
	Quartile 2 (7.39-11.04%)	18	69	9	0			
	Quartile 3 (11.04-17.04%	0	17	64	8			
	Quartile 4 (≥17.05%)	0	0	16	65			
NRI=0.0129 P=0.86								0.0129

Clinical= age, gender, Charlson and BMI

Chapter 10

Therapeutic Guidance from Screening

Article "Imaging Guided Cardio-Protective Treatment in a Community Elderly Population of Stage B Heart Failure – a Randomized Controlled Trial" was published

JACC cardiovascular Imaging 2017; 10 (3): 217-226.

Hong Yang, Kazuaki Negishi, Ying Wang, Mark Nolan, Thomas H Marwick

Chapter 10. Intervention Responses to Screening

Introduction

The previous chapters focused on possible screening tools and the most effective screening strategy. However, it is unknown whether a screening program would be effective in reduction of heart failure even if the efficacy of screening for stage B heart failure was demonstrated[75,77]. One of the major challenges needed to justify an effective screening programs is "Do persons with positive screening comply with advice and interventions" [75]. This chapter sought to evaluate the effectiveness of imaging guided care compared to usual care in improving outcome in TasELF study.

The following text in this chapter has been published in ***JACC. Cardiovascular imaging 10(3): 217-226.***

Abstract

Background. The detection of non-ischemic stage B heart failure (SBHF) has been facilitated by advanced echocardiographic imaging modalities. However, improved outcomes have not been proven as they are predicated on benefit of treatment.

Objectives. The purpose of the study was to evaluate the benefit of care guided by the detection of SBHF using advanced echocardiography for the reduction of new HF in the community.

Method. Between 9/2013 and 11/2015, 618 asymptomatic community-based patients with HF risks (age 71±5 years) were randomized to care guided by advanced echocardiography (AE; myocardial deformation and detailed diastolic function) versus usual care (UC). Evidence of SBHF led to advice to the patient and their primary physician to initiate treatment with angiotensin converting enzyme inhibition and beta adrenoceptor blockade. The trial followed Prospective Randomized Open Blinded Endpoint design. Participants were followed for 1 year for the primary composite endpoint of death from cardiovascular causes and new HF.

Results. AE identified 219 as having SBHF and treatment was advised. Over a mean follow-up of 13±6 months, 67 reached the primary end-point. The incidence rate of HF was no different between the two arms (p=0.47), likely because only 43% initiated therapy, and only 9% achieved target dose. Among subjects needing therapy on the basis of imaging and adherent to therapy, imaging guided care showed a 77% lower hazard for the primary outcome (p=0.04).

Conclusion. The detection of SBHF from strain and diastolic function evaluation was associated with a higher incidence of incidence HF and death. The efficacy of pharmacological intervention with angiotensin converting enzyme inhibition and beta-adrenoceptor blockade is limited by its uptake, and alternative strategies should be considered.

10.1 Background

Stage B heart failure (SBHF), has been defined in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines to include asymptomatic patients with abnormal left ventricular (LV) structure or function [25]. Patients with SBHF are at higher risk for developing overt heart failure (HF)[44]. In contrast to Stage A HF (SAHF, i.e. HF risk factors) [333], where therapy is directed towards the control of cardiovascular (CV) risk factors, cardio-protective therapies are recommended in SBHF [25], on the basis of trials showing pharmacological interventions to delay and reduce the burden of HF in the SBHF population [40,41]. The difference between SAHF and SBHF is a problem, because although highly prevalent, non-ischemic SBHF requires an effective screening strategy for its recognition. While modern imaging techniques may be able to provide this strategy, their incorporation into routine care needs evidence that management will be altered.

10.2 Aims and Hypothesis

Accordingly, we developed a community-based screening program in elderly patients for detection of SBHF using echocardiography and subsequent cardio-protection. Our primary aims were: 1) to assess whether imaging guided cardio-protective therapy, when added to usual care, would reduce the rate of incident heart failure, 2) to assess the feasibility of coupling an effective community screening program with interventional treatment in high risk asymptomatic elderly individuals with SBHF.

10.3 Methods

Study design. The Tasmanian Study of Echocardiographic Detection of LV Dysfunction (TasELF) is a community based screening and interventional program. The study followed a Prospective Randomized Open Blinded Endpoint (PROBE) design [186]. Individuals were randomized to either undergo an imaging guided screening strategy for early detection and treatment of SBHF or to continue with usual care [334]. The data were collected at various clinical sites within the State of Tasmania, Australia.

Patient selection. Asymptomatic community-based patients (≥65 years old) with HF risks volunteered for enrolment through local community presentations and media advertising. Patients with stage A HF risk factors were eligible for inclusion[25], including hypertension (HTN, based on blood pressure ≥140/90 mmHg and self-report of HTN including anti-hypertensive medication); type 2 diabetes mellitus (T2DM, based on self-report of diagnosis including medical management); obesity (body mass index [BMI] ≥30); previous chemotherapy; family history of heart failure; previous history of heart disease (but not existing heart failure). We excluded subjects with: symptoms or a known history of HF; known coronary artery disease (CAD); more than moderate valvular heart disease; reduced left ventricular ejection fraction (LVEF) (<40%) on baseline echo; already taking both trial medication, beta-blocker (BB) and angiotensin converting enzyme inhibitor (ACEi)/Angiotensin Receptor Blocker (ARB), at baseline and contraindication of BB and/or ACEi and ARB. We also excluded those in whom we were unable to acquire interpretable images from baseline echocardiography (inclusion and exclusion in Table appendix 10.59).

End-point. The primary composite endpoints were incident HF and death from CV causes. Potential HF symptoms were assessed through regular follow-up phone calls, followed by symptom surveillance questionnaires and clinical visits. New onset HF was adjudicated by a blinded end-point committee using Framingham criteria at 1 year. Loss to follow-up was defined as not having replied for evaluation in ≥2 months.

Sample size. Sample size was calculated based on the following: 1) an expected prevalence of abnormal cardiac function in ~50% using advanced echocardiographic imaging, 2) an expected 7.5% annual rate of loss to follow-up, 3) a previously reported 12% annualized rate of incident heart failure among patients with evidence of SBHF under usual care [57], 4) assumption of a

50% reduction of events with intervention compared with usual care. A sample size of 400 in each randomized group would provide 80% power to document benefit of therapy at a two sided α=0.05.

The trial was monitored by a Data and Safety Monitoring Board (DSMB) with termination guidelines for futility (if conditional probability of rejecting the null hypothesis was unlikely to achieve statistical significance) and feasibility (if recruitment or other aspects of its conduct were unable to fulfil requirements due to unforeseen circumstances.

Randomization. Randomization was done using central web-based program with adaptive allocation stratified by diabetes status. The eligible participants were randomized to advance echocardiographic imaging (AE, involving measurement of global longitudinal strain and diastolic function), versus usual care (UC, continuing with their usual care treatment for primary risk factors such as hypertension and diabetes). The randomization list and intervention list were prepared by assigned persons who were blinded to details of the investigations.

Patient report outcome measures (PROMs) and functional capacity. All participants enrolled in the study underwent a physical examination and standard PROMs questionnaires relating to health status (EuroQol 5 Dimensions Index, EQ5D), activity status (Duke Activity Score Index, DASI), symptom status (Minnesota Living with HF Questionnaire, MLHFQ), depression (Patient Health Questionnaire-9, PHQ9) and anxiety (generalized anxiety disorder questionnaire, GAD7).

Functional capacity was assessed using a 6-minute walk test (6MW) distance following a standardized protocol [209].

Echocardiographic study. Standard transthoracic 2D and Doppler echocardiographic studies were performed using standard equipment (Siemens ACUSON SC2000, Siemens Healthcare, Mountain View, CA) and transducer (4V1c, 1.25-4.5 MHz; 4Z1c, 1.5-3.5 MHz) in accordance with the American Society of Echocardiography (ASE) guidelines[187]. Diastolic function was assessed by measuring mitral inflow peak early diastolic velocity (E), peak late diastolic velocity (A), E/A ratio, E wave deceleration time (DecT)[188,189,281]. Echo left ventricular hypertrophy (LVH), left atrial enlargement (LAE) was assessed according to recommended cutoffs [187]. Diastolic dysfunction (DD) grade was defined as previously described[189,281]. Grade

I: E/A <0.8, E/e'<10, pulmonary venous inflow S<D. Grade II: 0.8<E/A<1.5, E/e' > 13 or LAE, or presence of mid diastolic forward flow (L wave), or positive Valsalva (> 50% increase of E/A ratio). Grade III: E/A> 1.5, DecT<140 ms. LV peak longitudinal strain measurements were obtained from gray scale-recorded images in the apical 4-chamber, 2-chamber and long-axis views. Strain was analysed using velocity vector imaging (Syngo VVI, Siemens Medical Solutions). GLS was measured on-line by averaging strain from the region of interest in three apical views. Impaired GLS was defined using cut-off of <18 % [85]. All echocardiographic measurements were obtained on-line before participants left clinic. Echocardiographic definition of SBHF was: 1) Impaired GLS (<18%) and/or 2) ≥grade I diastolic dysfunction.

Cardio-protective treatment for SBHF. The treatment protocol was a combination of ramipril (starting with 1.25 and up titrate to 10 mg/day) with the addition of Metoprolol (start 12.5 and up to 100 mg/day) (titration plan in Appendix T2). Cardioprotection was initiated by the patient's general physicians (GP), under guidance by the investigators. The titration plan and guidance for monitoring was proposed to subjects with evidence of SBHF who required treatment in AE arm and their physicians. As some patients were already on one of the two agents (at submaximal dose) at recruitment, any pre-existing ACEi/ARB or BB, other than ramipril and Metoprolol, were up-titrated to the maximal tolerable dose (Table appendix 10.60).

General guidance regarding risk reduction was shared with all subjects, and a report (including clinical and imaging information, according to randomization arms) was shared with all patients and their physicians.

Medication adherence. The primary analysis involved comparison on an intention to treat basis, in the belief that this would provide direct evidence of the clinical effectiveness of screening for SBHF.

Those who required treatment based on results of AE were notified of this at the screening visit and re-contacted within 4-6 weeks to reinforce the need to follow-up with their GP.

A process evaluation was performed within a period of 3 months, to allow reasonable time for up titration. Adherence to protocol was defined on the basis of treatment initiation and dose maximization.

Statistical analysis. Data are presented as mean (± standard deviation [SD]) after testing for normal distribution (Shapiro-Wilk test). Data deviating from normality are expressed as median (inter-quartile range [IQR]). Categorical variables are expressed as percentages. All analyses were performed on an intention to treat basis. The comparability of baseline characteristics in the two arms was assessed by chi-square tests for categorical variables and the Mann-Whitney U test for continuous variables. Cox proportional hazard regression model with time-dependent covariates was used to assess the relative risk of primary outcome of individuals under usual care versus those under imaging guided care. Survival analysis was performed using the Kaplan-Meier method, and the differences in survival between groups were assessed by the log-rank test. Statistical analyses were performed using a standard statistical software package (SPSS software 22.0, SPSS Inc., Chicago, IL). Statistical significance was defined by $p<0.05$.

This report follows the recommendations of the 2010 Consolidated Standards of Reporting Trials Statement [335]. This study was performed in accordance with a research protocol approved by the Tasmanian Human Research Ethics Committee (HREC), and registered with the Australian and New Zealand Clinical Trials Registry (http://www.anzctr.org.au/; ACTRN12614000080628). Individual written informed consent was obtained from participants after explanation of the nature and purpose, complexity and level of risk of the study.

10.4 Results

Patient selection and characteristics. Between September 2013 and November 2015, a total of 1026 self-referred community participants at or over the age of 65 years, and with non-ischemic HF risk factors, volunteered in response to advertising through community organizations and local media. After clinical and echocardiographic screening for eligibility, 618 (age: 71±5 years, 48% men) met inclusion criteria. The most common HF risk factors were hypertension (79%), diabetes mellitus (51%) and obesity (44%), 79% of individuals having ≥2 of the listed risk factors. Of the total, 6.5% of participants were already taking BB and 67% were on ACEi or ARB treatment at baseline; none were taking both at baseline and none were at maximal doses.

Of these 618 individuals who underwent randomization, 308 were assigned to the advanced echocardiography-guided care arm (AE). The remaining 310 were assigned to the usual care

(UC) arm (Figure 10.58). There were no differences in the demographic, clinical, socio-economic features, nor were the patient reported symptoms and activity status between the two groups (Table 10.56). There were 23 patients who were in AF at baseline, 12 in AE arm and 11 in UC arm. Of the 12 in AE arm, all had abnormal GLS and treatment was required based on abnormal GLS. None of 11 AF of UC arm required treatment for abnormal EF.

Screening results and pharmacological intervention. Comprehensive echocardiograms were performed in all subjects. Of the 308 individuals in AE arm, evidence of SBHF was found in 219 (71%) defined by abnormal GLS or DD, with abnormal GLS present in 113 (37%) and diastolic dysfunction in 211 (69%); 83 individuals (27%) had both. Patients with abnormal function were older and had significantly higher Atherosclerosis Risk in Communities (ARIC) HF risk score and Charlson comorbidity score compared with the remaining AE patients ($p<0.002$). Treatment advice with titration plan were proposed to these 219 as well as their GP. There were 18 patients in the AE group who had a mid-range EF (40-53%), of whom 17 required treatment on the basis of abnormal GLS or DD. Of the 310 individuals in UC arm, no treatment was advised based on GLS and DD criteria. However, 5 individuals were started on treatment based on mild reduction of left ventricular ejection fraction (LVEF 40-53%); none had LVEF <40%.

Side-effects. Side-effects were self-reported in a total of 31 individuals, but there was no reported syncope or other severe adverse effects. The most common side-effects were dry cough from Ramipril and bradycardia and lethargy from beta blocker. Side-effects led to discontinuation of the medication in 4% in the AE arm and none in the UC arm, with most continuing with minor adjustment of medication. Side-effects were also reported in individuals in usual care group. These are summarized in Table 10.58.

Intention-to-treat analysis. At the last follow-up clinic (March 2016), 23 (11 from AE) participants were contactable but unable to attend the follow-up assessment. Contact was lost with 8 participants (1.3%) - 4 from the AE arm. At 13±6 months, a total of 22 (4%) participants (18 from the AE arm and 4 from the UC group) had withdrawn from the study because of reluctance to attend further follow-up, unwillingness to take additional medication, but in only 3 due to side-effects. Therefore, follow-up for this outcome assessment was 91% complete (275 vs 290/618) (Figure 10.58).

There were 5 deaths (2 of cardiovascular causes). New HF symptoms developed in 65 patients. The primary composite end-point of new HF and CV death occurred in 67 (11.8%) with an annualized incidence rate of 10.9%. The three deaths from non-CV causes were in both arms while the two CV deaths were both in the AE group. The incidence of the primary end point was 13% (37/275) in the AE arm and 10.3% (30/290) in the UC arm (p=0.25). There was no difference in event free survival using Kaplan-Meier analysis between two arms (Log rank Chi-square=0.53, p=0.47) (Figure 10.58).

Initiation and up-titration of medication. Medication initiation and up-titration was assessed using self-reporting questionnaires and telephone calls. Almost all patients - 307 of 308 in the AE arm and 309 of 310 from the UC arm - responded to our evaluation. Figure 10.60 summarizes medication status in the entire cohort. An increment of medical therapy (determined by initiation or up-titration) was achieved in total of **146** individuals across both arms. In the AE arm, an adjustment of medication was achieved in **94** out of the **219 (43%)** SBHF patients with abnormal imaging (Figure 10.60). Of these 219 subjects, **20 (9%)** had achieved recommended target dose, and **64** had initiated one or both medications without dose increments because of concern about reduction of BP or other potential sources of intolerance. The cut-offs dose as target dose were: Ramipril 10 mg/day; Enalapril 20 mg/day, Perindopril 10 mg/day. Irbesartan: 300 mg/day; Candesartan 32 mg/day; Valsartan 160 mg/day; Metoprolol: 100 mg/day. For other reasons (generally blood pressure control) an adjustment of medication was also achieved in 15% of the UC arm, and in 7 subjects in the AE arm without evidence of SBHF.

The DSMB stopped the trial in November 2015, on the basis of poor therapeutic adherence (~40%) in both initiation and up-titration of medication.

Protocol analysis. The potential clinical benefit of screening guided care was evaluated in Cox proportional hazard model and with the adjustment of number of subjects who required treatment. Given the fact that a low medication adherence (43%), the model was also adjusted for subjects who were actually adherent to treatment (Treatment up-titration). Echocardiographic imaging guided care was associated with 77% lower risk for primary outcome at one year, hazard ratio 0.23 (95% CI 0.06-0.98, p=0.047) (Table 10.58).

In the absence of treatment protection, individuals with abnormal GLS, diastolic dysfunction and the presence of both was associated with worse outcome (Figure 10.61). No treatment benefit were observed in subgroups with Abnormal GLS, DD and the presence of both (p>0.4).

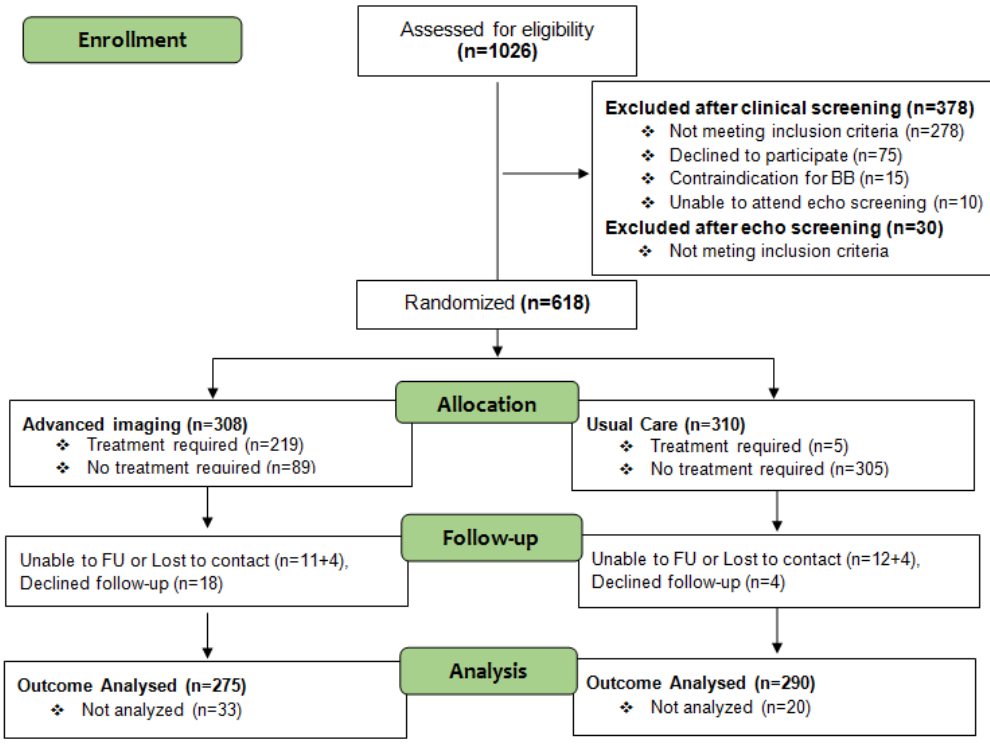


Figure 10.58 Consort diagram

CONSORT chart describing patient allocation. Patients were randomized to imaging guided care, advanced echocardiography (AE) or usual care (UC), guidance was given based on the findings of echocardiography.

Table 10.56 Baseline characteristics
Clinical, social economical and echocardiographic characteristics of two randomized groups - “usual care, UC” versus “advanced echocardiography, AE”.

	UC (n=310)	AE (n=308)	p value
Demographic and clinical characteristics			
Age (year)	70 (67-74)	70 (67-74	0.22
Age>75 year, n (%)	54 (17)	54 (18)	0.97
Gender male, n (%)	140 (45)	152 (49)	0.29
Body Mass Index (g/m^2)	29 (26-32)	29 (26-33)	0.89
Systolic blood pressure (mmHg)	140 (128 (150)	140 (129-149)	0.88
Diastolic blood pressure (mmHg)	82 (75-89)	81 (75-88)	0.58
Ever Smoking, n (%)	152 (49)	150 (49)	0.93
ARIC score (%)	5.8 (3.7-10.7)	6.3 (3.4-11.9)	0.67
T2DM, n (%)	158 (51)	155 (50)	0.87
Obese, n (%)	139 (45)	135 (44)	0.8
Hypertension, n (%)	243 (78)	243 (79)	0.88
Previous Chemotherapy, n (%)	32 (10)	43 (14)	0.17
Family history, n (%)	107 (35)	117 (38)	0.37
Previous heart condition, n (%)	25 (8)	26 (8)	0.87
Charlson score	1.0 (0-2)	1.0 (0-2)	0.52
ACEi, n (%)	208 (67)	208 (68)	0.91
Beta-blocker, n (%)	19 (6.1)	14 (4.5)	0.38
Calcium Antagonists, n (%)	60 (21)	70 (25)	0.32
Diuretics, n (%)	44 (15)	35 (12)	0.31
Lipid lowing medication, n (%)	166 (58)	149 (52)	0.19
Anti-platelets, n (%)	107 (37)	105 (37)	0.94
6 minute walk distance (meters)	485 (432-546)	480 (410-530)	0.19
Patient report outcome measures (PROMs)			
Duke activity score index (MET)	8.3 (7.3-8.9)	8.3 (7.0-8.9)	0.94
General Health utility (EQ5D)	0.84 (0.74-1.0)	0.84 (0.77-1.0)	0.62
General Health utility (EQVAS)	80 (70-90)	80 (70-90)	0.82
Minnesota Living with HF score	1 (0-8.3)	1 (0-8.0)	0.62
Depression status (PHQ9)	2 (0-4)	1 (0-3)	0.24
Anxiety status (GAD7)	1 (0-3)	0 (0-2.8)	0.26
Socio-economic determinants			
Social economical index for areas (ranking 1-10)	4 (2-6)	4 (2-6)	0.48
Education level ≥ high school, n (%)	245 (83)	247 (82)	0.76
Living alone, n (%)	90 (30)	107 (36)	0.12
Private Health insured n (%)	216 (72)	211 (71)	0.79
Total Number of medication pills /day	5 (3-8)	5 (3-8)	0.46
Baseline echocardiographic characteristics			
Valve disease*, n (%)	11 (3.5)	13 (4.2)	0.67
Left ventricular ejection fraction (%)	64 (60-68)	64 (60-68)	0.75
GLS (%)	18.5 (16.7-20.3)	18.4 (16.8-20.1)	0.67
E/e' (average)	8.4 (7.1-10.3)	8.4 (7.1-10.3)	0.66
Abnormal GLS (18 cutoff), n (%)	103 (33)	113 (37)	0.37
Diastolic dysfunction (≥ grade I), n (%)	206 (67)	211 (69)	0.58
Diastolic dysfunction (≥ grade II), n (%)	43 (14)	41 (13)	0.92
Left ventricular hypertrophy, n (%)	42 (14)	39 (13)	0.74
Left atrial enlargement, n (%)	117 (38)	104 (34)	0.29
Abnormal E/e', n (%)	39 (13)	34 (11)	0.55

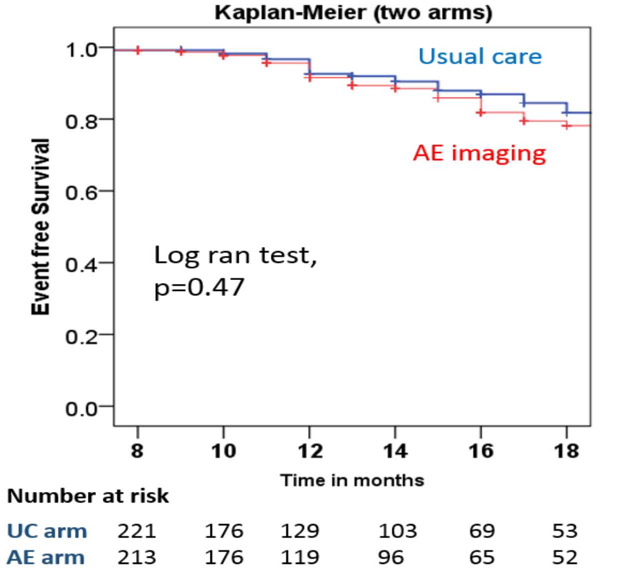


Figure 10.59 Kaplan-Meier analysis of event free survival between two arms

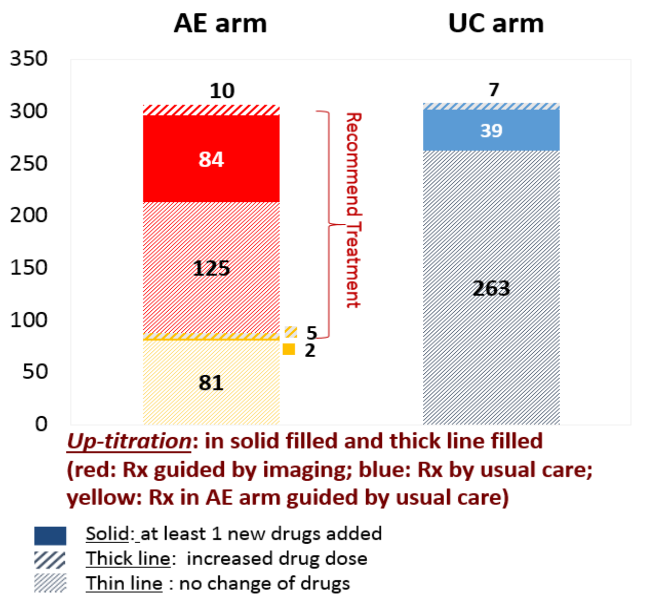


Figure 10.60 Medication status at follow up

In the AE arm, an increment of medication was achieved in 84 out of the 219 (43%) SBHF patients with abnormal imaging (shown in red). In addition, 7 subjects in the AE arm (labelled in blue) had cardioprotective medications started for control of hypertension, without evidence of SBHF. An increment of medication was also achieved in 14% of the UC arm,

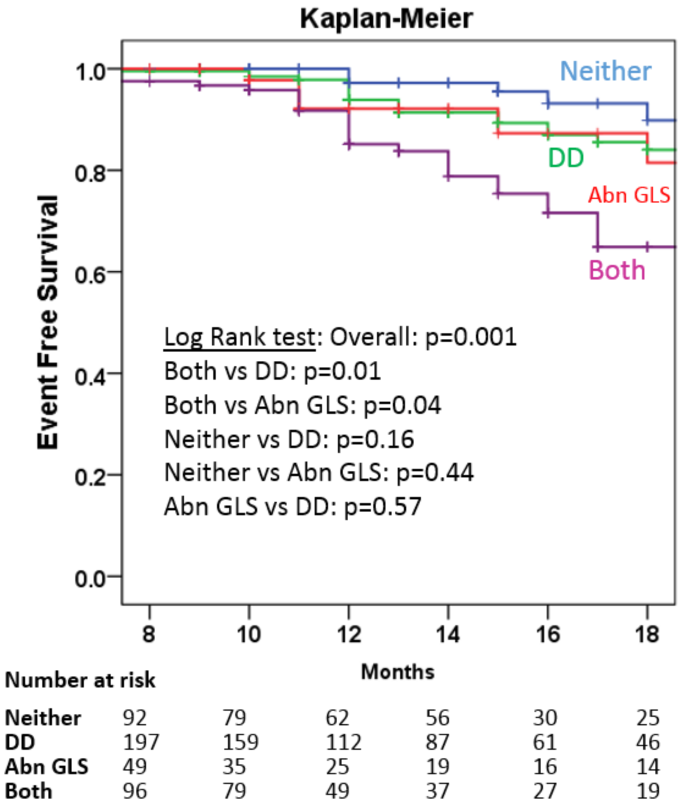


Figure 10.61 Kaplan-Meier analysis of outcome between GLS vs DD

Table 10.57 Clinical effect of screening for primary outcome

		Crude		**Adjusted****	
	No. of endpoints/ total assessed* (%)	HR (95% CI)	p value	HR (95% CI)	p value
New HF and CV death					
Advanced Imaging (AE) versus Usual care (UC)	37/275 (13%) 30/290 (10%)	1.22 (0.75, 1.97)	0.43	0.23 (0.05, 0.95)	0.04
SBHF identified by imaging versus SBHF not identified or unknown	35/219 (16%) 32/346 (9%)	1.99 (1.23, 3.23)	0.01	7.01 (1.65, 29.9)	0.01
Treatment up-titration (+) versus Up-titration (-)	24/143 (17%) 43/422 (10%)	1.51 (0.91, 2.49)	0.11	1.09 (0.64, 1.86)	0.75

* A total of 565 out of 618 were assessed for primary outcome at 1 year follow up
**Adjusted for (in the model as binary variables): randomization status + SBHF by imaging + Treatment up-titration

Table 10.58 Medication side effects and alterations

	AE arm	UC arm	total
ACEi/ARB			
no change in dose	7	2	9
reduce dose	0	0	0
ceased but stay on trial	2	0	2
ceased and wish to withdraw	1	0	1
Beta blocker			
no change in dose	8	1	9
reduce dose	2	2	4
ceased but stay on trial	2	1	3
ceased and wish to withdraw	3	0	3
total	25	6	31

10.5 Discussion

The results of this study show that among individuals in the community ≥65 years old, with mainly multiple HF risk factors, evidence of SBHF was identified in 71% with the use of advanced echocardiography, and these showed an annualized event-rate of 10.9%. Despite the prognostic information from imaging, the trial emphasizes the difficulties in providing cardio-protection in asymptomatic elderly individuals at risk of HF. Pharmacological intervention was unsuccessful in intention to treat analysis, although there may have been potential benefits from imaging-guided care in adherent patients.

Definition of new HF. Heart failure is a clinical diagnosis, and patients may minimize or deny their symptoms in the early phases, making clinical recognition difficult. Prevalence estimates may vary broadly depending on the diagnostic criteria; a recent meta-analysis reported that incident HF diagnosis in 8 of 15 included studies was based on a non-standardized clinical description [273].

Differences in the diagnostic criteria for HF may also impact the outcome assessment in these studies. Among four commonly used HF diagnostic criteria (Framingham, Boston, Gothenburg, and European Society of Cardiology (ESC) criteria) [312], there were significant differences in predicting clinically relevant outcomes including incident hospital admission. As disturbances of cardiac structural and functional characteristics at baseline were best predicted using the Framingham HF criteria [312], we selected the Framingham HF criteria to adjudicate events in our study. However, although the absolute 3-year risk of hospital admission following a Framingham HF diagnosis was 6.1% (odds ratio 6.9, 95% CI 1.3-36.1, p=0.022) [312], the annualized rate of incident HF in our study was 10.3%. This likely reflects the high clinical risk of these subjects, most of whom had multiple HF risk factors. In addition, although we excluded symptomatic HF at entry, Framingham criteria may not capture mild or early HF (stage C1) in individuals with atypical symptoms[44]. Moreover, a high rate of incident HF was observed in a similar community study of a cohort with combined diabetes and hypertension [57], in whom E/e' > 15 (detected in 23%) was used to categorized stage B HF. In our cohort, the prevalence of increased E/e' was similar in those with both HTN and T2DM (20%).

Diagnosis and management of SBHF. Imaging screening for SBHF is based on the concept that this stage is a precursor of overt clinical HF, and has been advocated in practice guidelines [336] because SBHF is associated with a 5-fold greater risk of symptomatic HF [82]. Imaging by echocardiography is generally believed to be a safe and accurate for the diagnosis SBHF. Although EF as the only functional feature in the conventional criteria for SBHF [152], both strain and diastolic dysfunction are associated with adverse outcome and impaired functional capacity [70].

Of course, the accuracy and prognostic value of diagnostic tests have no direct effect on patient outcomes unless indirectly by influencing the therapeutic pathway. The evidence to date for pharmacological therapy in SBHF is largely based on EF. This supports ACEi as the foundation of management of SBHF [34], with the improvements in all-cause mortality, recurrent cardiovascular events and progression to HF [37,88]. In the Heart Outcomes Prevention Evaluation study (HOPE) [42], ACEi also significantly reduced the rate of death, myocardial infarction, and stroke, and reduction of HF admission and death was reported after treatment in a similar population with SAHF [337]. Evidence also supports the use of beta blockers in asymptomatic patients [34]. In the Survival and Ventricular Enlargement (SAVE) and Studies of Left Ventricular Dysfunction (SOLVD) trials, concomitant use of beta blocker therapy was associated with reductions in cardiovascular death and heart failure [37,88].

In this study, we sought to gather evidence on the benefit of early detection of SBHF using new functional markers to guide management. We assessed this by randomizing subjects to either screening strategy or usual care and comparing their outcomes, using an “intention to treat” approach [334]. This design allows assessment of the benefit of early detection, as well as recognition of potential risks associated with diagnostic procedures, including false positives resulting in over treatment. In addition, our intention was also to determine whether an intervention works among a community screening population. Unfortunately, the negative results of the current study were attributable to lack of effectiveness [338] in medication delivery following imaging screening. Side-effects were uncommon, and the main causes were reluctance of patients and physicians to initiate and up-titrate therapy in the presence of a normal EF and the absence of symptoms.

10.6 Study Limitation

This study has several limitations. The follow-up time was only one year. The method adopted for assessment of medication use was self-report rather than pill counts and rate of prescription refills. However, there is no optimal means of achieving this [339], and self–report is simple and feasible in the context of community screening and has been strongly associated with adverse cardiac events [340].

We excluded patients with EF <40% because previous clinical trials showed a benefit from therapy (30). The study did not incorporate the analysis of HF with mid-range EF, a category that has been recently proposed in the guidelines (31), and only one patient was in this category in the absence of abnormal GLS.

AF was not excluded in the initial design, because the optimal management of this important subgroup in non-ischemic stage B HF is unclear. However, the numbers of patients with AF was small, and they were equally distributed among the groups. Of the 12 in AE arm, all had abnormal GLS and treatment was required based on abnormal GLS. None of the 11 AF patients in the UC arm required treatment for abnormal EF.

10.7 Conclusion

The application of advanced echocardiographic markers is feasible in the community diagnosis of SBHF, and predicts incident HF. Despite their risk levels, the adherence to intervention in this asymptomatic group with a normal EF was poor. Subsequent attempts with this study design might include a disease management program to ensure adherence with therapy.

Clinical Perspectives:

Competency in Medical Knowledge. Patients of >65 years old with heart failure risk factors have a high prevalence of stage B heart failure, evidenced by LV hypertrophy, LV diastolic or systolic dysfunction. These patients are at risk of early development of clinical heart failure.

Competency in Patient Care. The appropriate therapeutic response to the detection of stage B heart failure is undefined. This study showed no benefit from screening for stage B heart failure, but uptake of cardioprotective therapy and dose titration were both inadequate.

Translational Outlook. A strategy to identify stage B heart failure seems unlikely to alter the progression to heart failure in the absence of an integrated disease management program.

Postscript

In the TasELF study, we proved that non-ischemic stage B heart failure is highly prevalent in the community. We also proved that an effective screening strategy in the community is feasible. However, we have not proven the benefit of imaging surveillance using advanced imaging tools. Poor compliance of patient to medication is the direct cause of premature cessation of this trial. The introduction of cardio-protection in asymptomatic individuals has potential system-, patient- and provider-level barriers. Previous studies have shown that about half of all patients prescribed antihypertensive medication stopped taking them within a year[350]. The non-adherence rate in HF patients is reported as 21% for ACEi, 35% for beta-blockers, 44% for spironolactone and 17% for statins[351]. The preparedness to initiate treatment is a barrier at provider-level. This includes perceived patient attitude, concerns over patient age, gender, comorbidity and clinical uncertainty[352]. These "soft" reasons to avoid management intensification are the main components of clinical inertia. At system level, problems in adherence may be ameliorated by increasing the involvement of the specialist in supporting primary care givers (e.g. disease management programs). The program can involve case managers and patient care teams[353], emphasis of evidence-based guidelines in flow sheets to monitor therapy, and improving the measurement of medication adherence[354].

Appendix Figures and tables

Table appendix 10.59 -Inclusion and Exclusion

Inclusion criteria

- Age: at least 65 years of age ($\geq$ 65 years)
- The presence of at least one of the following 1) Hypertension, based on SBP>140 mmHg and self-report of HTN including anti-hypertensive medication; 2) type 2 diabetes mellitus, based on self-report of diagnosis including medication; 3) obesity, based on body mass index (BMI) $\geq$ 30 g/m2; 4) previous potentially cardio-toxic chemotherapy; 5) familial cardiomyopathy; 6) previous history of heart disease (but not existing heart failure).

Exclusion Criteria

- Unable to provide written informed consent to participate in this study
- History of previous heart failure, baseline NYHA >2
- History of coronary artery disease (previous myocardial infarction, myocardial revascularization, Coronary stents, positive stress test. Or echocardiographic screening of LVEF<40%. (These are either known coronary artery disease or underlying coronary artery disease)
- Known history of more than moderate valvular heart disease
- Systolic BP <110mmHg, pulse <60/minute
- Serious life-threatening disease (anticipated life expectancy <2 years)
- Pre-existing treatment with both *investigational drug (ACEi/ARB and Beta blocker*) classes or one class at maximum dose
- Contraindications/Intolerance of either beta blockers or ACEi/ARB,
- Participating in any other clinical research trial
- Inability to acquire interpretable images (identified from baseline echo)

Table appendix 10.60 -medication titration schedule

Weeks from start	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**
Ramipril (mg/d)*	1.25	2.5	5	5	5	5	5	5	10
Metoprolol (mg/d) **			12.5	25	37.5	50	75	100	

*If patient is already on an ACEi or ARB, there no need to change, however, please up-titrate to the maximal tolerable dose.
** If patient is already on another B-Blocker, there is no need to change, please up-titrate to the maximal tolerable dose.

During treatment, patients need to be seen every 2 weeks during the up titration phase. At each of these visits, symptoms status (fatigue, dizziness), blood pressure and heart rate need to be obtained. If patients complain of side-effects or the heart rate is <50 beats per minute, the dose should be reduced to the prior to the last increment.
Discontinuation criteria: symptoms consistent with cardiac dysfunction (dyspnea, reduced exercise capacity), side effects of therapy (fatigue), progression of cardiac dysfunction (EF<50%, dyspnea, reduced exercise capacity)

Chapter 11

Summary

Conclusion

Future direction

Chapter 11. Summary future direction and conclusion

11.1 Summary of background

Heart failure is a major burden to the health care system and the community due to the cost of care and poor quality of life. The prevention of heart failure might be possible with early identification and early intervention to reduce the disease burden.

Stage B heart failure is the precursor stage of clinical heart failure. However, causes of stage B heart failure are heterogeneous as are the underlying pathophysiological changes. Previous clinical trials have provided us evidence in the ischemic population using pharmacological intervention. However, the majority of the Stage B heart failure in the community is now of non-ischemic aetiology.

Asymptomatic stage B heart individuals in the community could be detected with an effective screening strategy based on modern imaging modalities. However, a screening program in the community is not only about the identification of the disease, but also about provision of a management service, including medical treatment and monitoring of these with positive test results. Medication adherence poses additional challenge for good communication to convey the prognostic impact of abnormal cardiac function in these seemly health individuals.

11.2 Summary of results

Speckle tracking imaging is a reliable imaging modality in the community. Being semi-automated and highly feasible for point of care assessment. Multiple echo markers provide incremental prognostic value over clinical information. Global longitudinal strain was a superior predictor of outcome to left ventricular mass, left atrial volume and mitral E/e'.

Second, in this elderly cohort at risk of heart failure, stage B heart failure was highly prevalent. The prevalence of any abnormal echocardiographic marker was 60-70%. The presence of this stage B is associated with 3-fold higher risk of new heart failure at one year follow-up.

Third, the screening for SBHF using echocardiography can be facilitated by an effective pre-screening strategy. Among those with the presence of stage A heart failure risk factors, calculation of risk can be obtained from clinical information and a 6-minute walk test at baseline. About 20% would be classified as high risk and echocardiography is indicated, and 40% will be classified as low risk and usual care would be advised. In the significant intermediate risk group of 40%, evaluation might involve ECG, but if resources allowed, echocardiogram may be beneficial, as half of the new heart failure came from this group.

Fourth, at one year follow-up, the incident rate of new heart failure was high, 104 per 1000-person year. Effective intervention in these community dwelling individuals is important.

Fifth, despite a high incident rate of new heart failure at one year, pharmacological intervention was not being successful in this trial. By process evaluation, only 9% of that requiring treatment had reached target dose, 34% initiated their therapy according to titration plan. Adherence was only 43% if based on the initiation or optimization of the titration plan.

Sixth, a semi quantitative process evaluation by questionnaire and telephone showed subjective unwillingness from both the participants and their physician seemed to be the main barrier to medication adherence. 22% of the entire cohort experienced some degree of financial pressures in paying their medical bills and this percentage was higher (34%) in non-adherents. Difficulties in obtaining medication were recorded in 7.5% overall, and 22% (p=0.008) in non-adherents. Non-adherence was not associated with age, gender, clinical characteristics and their societal economic factors in this cohort.

Last, subclinical cardiac dysfunction is also present in otherwise healthy but overweight and obese young adults. While cardiac structural changes are associated with their childhood weight status, cardiac dysfunction was mostly associated with their current weight status and the magnitude of weight gain from childhood. Future studies may explore the duration and magnitude of weight change with events as well as the association of their subclinical cardiac dysfunction with future events.

11.3 Strengths and Limitations

To our knowledge, this is the first study in the literature; on community screening and cardio-protection for non-ischemic stage B heart failure. It is also the first intervention study using advanced imaging (strain imaging and comprehensive diastology) modality in the community.

The main limitations of this trial have been discussed in each relevant chapter and as follows:

1). Recruitment through self-selection inherently carries a risk of population selection bias.

2). Short follow-up time. This is an on-going study; more results will be provided.

3). A relatively high event rate at one year, suggesting possible unrecognized symptoms at baseline by participants as they are non-specific and not meeting heart failure definition.

4). Non-ischemic status was based on self-report of history, but a stress test was not performed due to the feasibility in the community, we cannot exclude an ischemic contribution to the cardiac changes.

5). The lack of protection of clinical outcome by treatment may indicate confounding by indication (most at risk patients were treated in primary care, but were more likely to have events.

6). Medication history and adherence were mainly self-reported as compared to pill counts and assessment of prescription refills.

7). We did not obtain biomarkers, although recent evidence in the literature showed controversial results on its performance.

8). Lack of intensive monitoring of the participants under treatment and intensive communication with their primary physician to reinforce adherence with specialist support. A preventive strategy may be successful with the implication of a disease management program (DMP).

9). Finally, the study samples in chapter 6, 7, 8, 9 and 10 were from TasELF population, there are some discrepancies in study samples in each chapter. One reason is that not all studies were conducted at same time the period of recruitment. Another important reason is the hypothesis in each chapter varies. Figure 11.62 is a general flow chart explaining the difference in patient selection in each chapter of this thesis.

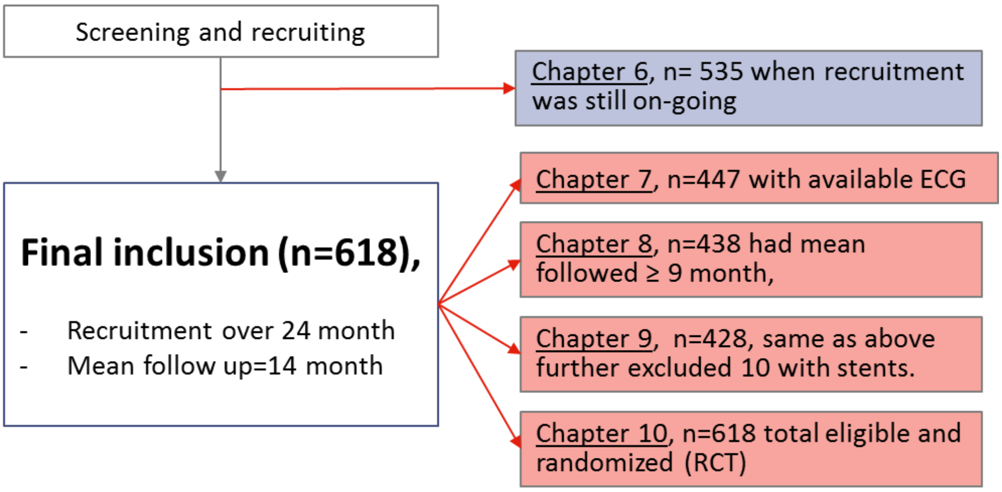


Figure 11.62 General flow chart of sample selection in chapter 6,7,8,9, and 10.

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11.4 Future directions

First, although echocardiographic markers including advanced imaging markers are powerful predictors of clinical outcome, their value in improving clinical outcome is predicated on treatment change. This has not been proven. Ensuring treatment adherence will be an important step to determine whether imaging guided treatment is efficacious and beneficial. To improve treatment adherence, effort may be made at the following levels: 1) At participant level, to provide a more individualized risk assessment including the absolute as well as relative risk with or without treatment. 2) At provider level, to provide a disease management program to facilitate management of elderly individuals with multiple comorbidities, medication intolerance and side effects.

Second, once prove an efficacious treatment, the cost-effective analysis of a community screening and early intervention program versus long term reduction of new heart failure incidence and reduction of heart failure hospitalization and management are important next steps.

Third, evidence on treatment and disease regression has been reported using echocardiographic markers, including reduction of left ventricular mass[341], left atrial volume[342] and improved global longitudinal strain[72]. These are important intermediate endpoints although these trials were performed in highly selected population with specific phenotype. These intermediate endpoints can be further assessed in this cohort and their association with heart failure and other cardio and non-vascular outcomes.

11.5 Conclusion

Diagnosis of SBHF need advanced imaging markers. Although advanced imaging markers are powerful predictors of clinical outcome in SBHF, the value of these markers in improving clinical outcome has not been proven, because it is predicated on treatment change. This is the critical first step - ensuring treatment adherence is important to determine that treatment is efficacious and beneficial. Once we prove an efficacious treatment, its cost to provide improvements in the short term and long term outcome need cost-effectiveness analysis.

The best strategy could be to use pre-screening using clinical information and feasible functional assessment to select high-risk individuals for echocardiography. Once abnormal cardiac function is detected, these individuals will be guided for treatment.

The whole screening process may be best accomplished in a disease management program, including trained nurses, sonographers, general physicians and specialist cardiologists to ensure treatment adherence, safety and screening effectiveness.

Heart failure prevention is important in the community. We have proved that an effective screening strategy in the community is feasible. We have also shown the high prevalence of stage B heart failure in the community. However, the benefit of imaging surveillance using GLS on therapy has not been proven.

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